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(54) **New tetrapyrrole polyaminomonocarboxylic acid therapeutic agents.**

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Description

This invention relates to new therapeutic compositions which are useful in photodiagnosis and phototherapy, especially in th d tection and treatment of tumors and cancerous tissues in the human or animal body.

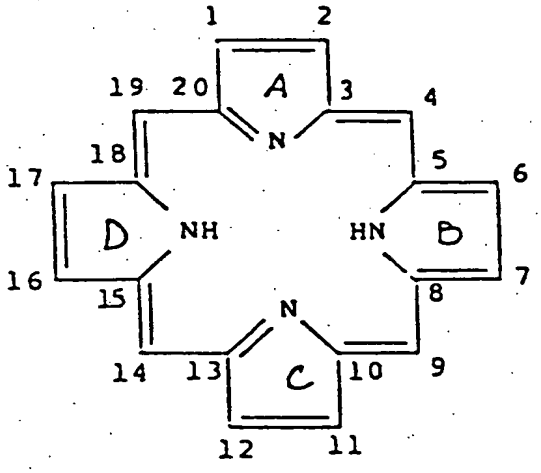
It is known to irradiate tumors and cancerous tissues in the human body with intensive light following administration of a hematoporphyrin derivative in the wavelength range of 626 to 636 namometers to reduce and, at times, destroy the cancerous cells (see PCT published specification WO 83/00811). It is also known that porphyrins, especially the sodium salt of protoporphyrins, can maintain or promote the normal functions of cells and are useful for preventing the genesis, growth, metastasis, and relapse of malignant tumors. Japanese Published Patent Application No. 125737/76 describes the use of porphyrins as tumor inhibiting agents, exemplifying etioporphyrin, mesoporphyrin, protoporphyrin, deuteroporphyrin, hematoporphyrin, coproporphyrin, and uroporphyrin.

In Tetrahedron Letters No. 23, pp. 2017 - 2020 (1978) describes an amino monocarboxylic acid adduct of the pigment bonellin obtained by extraction of principally the body wall of the marine echuroid B. viridis. The structure of these adducts is presumed to be an amide formed through either of the free carboxy groups of bonellin and the amino mono-carboxylic acid. Hydrolysis of the adduct yielded a mixture of valine, isoleucine, leucine and alloisoleucine. No use for these amino acid adducts is described in this reference.

That the tetrapyrroles cause intense photosensitivity in animals in well known and has been documented in numerous articles in literature, e.g., J. Intr. Sci. Vitaminol, 27, 521-527 (1981); Agric. Biol. Chem., 46(9), 2183-2193 (1982); Chem. Abst. 98, 276 (1983) and 88 6976m (1928).

EP-A-0142732 describes pheophorbide derivatives and alkali metal salts thereof as useful compounds in cancer treatment.

The therapeutic agents contemplated by this invention are cyclic tetrapyrroles derived by various procedures from naturally-occurring tetrapyrroles. The cyclic tetrapyrroles have as their common parent tetrapyrrole, uroporphyrinogen, and possess the following ring structure:



in which the positions in the molecule are numbered 1-20, and the rings identified by letters A, B, C and D, and also include perhydro-, e.g., dihydro- and tetrahydro-, derivatives of the said ring structure, e.g., compounds in which one or more double bonds are absent. There are present in the ring system four pyrrole rings joined through the alpha positions of the respective pyrrole rings by a methine group, i.e., -CH=. The compounds of the present invention are designated as derivatives of the tetrapyrroles for convenience in the disclosure and the appended claims and it will be understood that the term "tetrapyrrole" will designated compounds of the characteristic ring structur designated hereinb fore as well as the corresponding perhydro derivatives.

The tetrapyrroles employed in the present invention are all derived by various means and various alteration procedures from natural tetrapyroles. The naturally occurring t trapyrroles hav as their common ancestor uroporphyrinogen III, a h xahydroporphyrin reduced at th bridge positions. For exampl , synthetic or biosynthetic derivatives or products of protoporphyrins IX or protoporphyrinogen IX are well-known

in the art (see, for xampl , Porphyrins and Metalloporphyrins, K. Smith Elsivier; The Porphyrins (Vols. 1-7) D. Dolphin, Academic Press; and Biosynth tic Pathways, Vol. III, Chapter by B. Burnham, editor D.M. Greenberg, Academic Pr ss).

The non-cyclic tetrapyrroles are commonly known as bile pigments and include, for example, bilirubin and biliverdin. These tetrapyrroles are also derived from protoporphyrin, e.g., as metabolic products in animals.

A further characteristic of the present new therapeutic composition is the presence of at least one amide linkage in a substituent at any of the numbered positions of the ring structure. These are present in the instant new compounds together with other substituents as defined hereinafter.

Subject matter of the present invention is therefore a therapeutic composition according to claim 1.

Preferred embodiments of this composition are subject matter of claims 2 to 5.

Further subject matter is the use according to claim 6.

Thus, the present invention contemplates the therapeutic compositions containing amino acid or peptide derivatives of compounds which contain the chromophore of porphyrins, chlorins or bacteriochlorins, as well as related porphyrin compounds. The peptide linkage involves a carboxy group of the chromophore-bearing compound and the amino group of the specified amino acid. The present new therapeutic compositions embrace, inter alia, derivatives of the tetrapyrroles which contain a free carboxy group. These derivatives include the major classes of tetrapyrroles: carboxy-containing porphyrins, chlorins, and bacteriochlorins, which are well-known to those skilled in this art.

The amino acid employed in the present invention to form the aforesaid peptide linkage are aminomonocarboxylic acids in which the amino group, of course, is located on a carbon atom of th monocarboxylic acid. The specific position of the amino group in the carbon atom chain is not critical, the only requirement that the amino group be available to form the requisite peptide linkage with the carboxyl group of the selected porphyrin. Thus, a variety of amino monocarboxylic acids are useful in the present invention, including serine, glycine, α-aminoalanine, β-aminoalanine, ϵ-amino-n-caproic acid, piperidine-2-carboxylic acid, piperidine-6-carboxylic acid, pyrrole-2-carboxylic acid, pyrrole-5-carboxylic acid, piperidine-6-propionic acid or pyrrole-5-acetic acid. These amino acids may be substituted with angular alkyl groups, such as methyl and ethyl groups, as well as other groups which do not adversely affect the capability of the amino group to form the peptide linkage, e.g., alkoxy groups, or acyloxy groups, and may also include additional amino groups. The preferred amino acids are the naturally occurring α-amino acids, serine, alanine, and glycine, which are readily available and up to the present, have provided the best results.

Exemplary compounds of the tetrapyrrole classes are illustrated in Table I in which the numbered positions of the tetrapyrrole ring structure are used to designate the position of the indicated substituent. The absence of double bonds in the ring system is designated under "dihydro" with each set of numbers (ring position) indicating the absence of a double bond between the designated positions.

TABLE I

	Ring Position									
			B		C		D			
PORPHYRIN	1	2	6	7	11	12	14	16	17	Dihydro
Coproporphyrin III	Me	Pr	Me	Pr	Me	Pr	H	Pr	Me	---
Deuteroporphyrin IX	Me	H	Me	H	Me	Pr	H	Pr	Me	---
Hematoporphyrin IX	Me	Me | -CH | OH	Me	Me | -CH | OH	Me	Pr	H	Pr	Me	---
Protoporphyrin IX	Me	V	Me	V	Me	Pr	H	Pr	Me	---
Photoprotoporphyrin IX (one of two isomers shown)	Me	V	-Me -OH	=CHCHO	Me	Pr	H	Pr	Me	6,7
Mesoporphryin IX	Me	Et	Me	Et	Me	Pr	H	Pr	Me	---
Transmesochlorin IX	H Me	H Et	Me	Et	Me	Pr	H	Pr	Me	1,2
Transmesochlorin IX	Me	Et	H Me	H Et	Me	Pr	H	Pr	Me	6,7

TABLE I - Cont'd.

	Ring Position									
	A		B		C			D		
PORPHYRIN	1	2	6	7	11	12	14	16	17	Dihydr
Chlorin e_4	Me	V	Me	Et	Me	CO_2H	Me	H / Pr	H / Me	16,17
Chlorin e_8	Me	V	Me	Et	Me	CO_2H	Ac	H / Pr	H / Me	16,17
Mesochlorin e_4	Me	Et	Me	Et	Me	CO_2H	Me	H / Pr	H / Me	16,17
Isochlorin e_4	Me	V	Me	Et	Me	H	Ac	H / Pr	H / Me	16,17
Mesoisochlorin e_4	Me	Et	Me	Et	Me	H	Ac	H / Pr	H / Me	16,17
Mesochlorin e_6	Me	Et	Me	Et	Me	CO_2H	Ac	H / Pr	H / Me	16,17
Bacteriochlorin e_6	Me	ACL	H / Me	H / Et	Me	CO_2H	Ac	H / Pr	H / Me	6,7 16,17

TABLE I - Cont'd.

PORPHYRIN	Ring Position A 1	2	B 6	7	C 11	12	D 14	16	17	Dihydro
Bacteriochlorin e_1	Me	ACL	H / Me	H / Et	Me	CO_2H	Me	H / Pr	H / Me	6,7
										16,17
Bacterioisochlorin e_1	Me	ACL	H / Me	H / Et	Me	H	Ac	H / Pr	H / Me	6,7
										16,17

Notes:

Me: $-CH_3$ (Methyl group)

Pr: $-CH_2CH_2COOH$ (Propionic acid group)

V: $-CH=CH_2$ (Vinyl group)

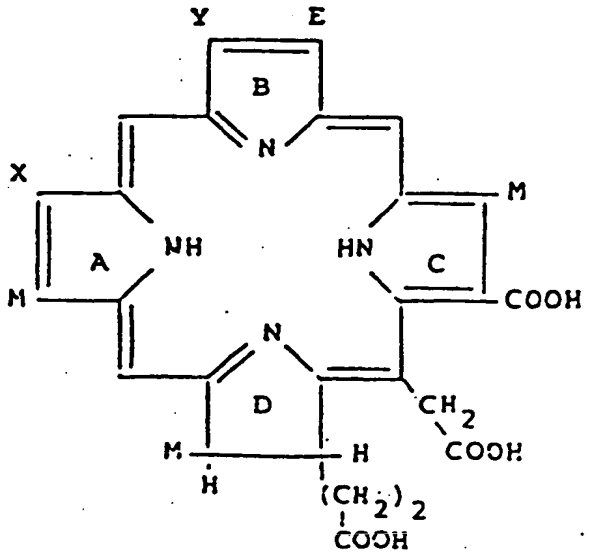
Et: $-CH_2CH_3$ (Ethyl group)

Ac: $-CH_2COOH$ (Acetic acid group)

ACL: CH_3-CO- (Acetyl group)

The preferred tetrapyrrole carboxylic acids are those wherein at least three carboxylic acid groups are present in the tetrapyrrole, preferably asymmetrically attached to the porphyrin ring system, e.g., the carboxylic acid groups are present on the rings A and B side of the molecule or on th rings D and C side of the molecule.

The particularly preferred therapeutic compositions comprise a fluorescent mono, di, or polyamide of an aminomonocarboxylic acid and a tetrapyrrol of the formula:



wherein;

X = H, vinyl, ethyl, acetyl or formyl;
Y = methyl or formyl;
M = methyl; and
E = ethyl

and pharmaceutically-acceptable salts thereof.

The compounds of the therapeutic composition form salts with either acids or bases. The acid salts are particularly useful for purification and/or separation of the final amide products as are the salts formed with bases. The base salts, however, are particularly preferred for diagnostic and therapeutic use as her in-described.

The acid salts are formed with a variety of acids such as the mineral acids, hydrochloric, hydrobromic, nitric and sulfuric acids, organic acids such as toluenesulfonic and benzenesulfonic acids.

The base salts include, for example, sodium, potassium, calcium, magnesium, ammonium, triethylammonium, trimethylammonium, morpholine or piperidine salts.

The acid and base salts are formed by the simple expediency of dissolving the selected amino acid tetrapyrrole amide in an aqueous solution of the acid or base and evaporation of the solution to dryness. The use of a water-miscible solvent for the amide can assist in dissolving the amide.

The final amide products can also be converted to metal complexes for example by reaction with metal salts. The magnesium complexes may be useful for the same purpose as the adduct product. Other metal complexes, as well as the magnesium complex, including, for example, iron and zinc, are useful to preclud contamination during processing of the adduct product by metals such as nickel, cobalt and copper, which are difficult to remove. Zinc and magnesium are readily removed from the final adduct product after processing is completed.

Since many of the aminomonocarboxylic acids exist in both the D- and L-forms, and also are employ d in mixtures of these forms as well as the D,L-form, the selection of the starting amino acid will, of course, result in products in which the respective isomer or mixture of isomers exist. The present invention contemplates the use of all such isomers, but the L-form is particularly preferred.

The present new compounds are prepared by the usual peptide synthetic routes which generally include any amide-forming reaction between the selected amino acid and the specific tetrapyrrole. Thus, any amide-forming derivative of the tetrapyrrole carboxylic acid can be employed in producing the present new peptides, e.g., lower alkyl esters, anhydrides and mixed anhydrides.

The preferred preparativ methods use mixed anhydrides of the carboxylic acid or carbodiimides. The reactants are merely contacted in a suitable solvent therefor and allowed to react. Temperatur s up to the reflux temperature can be used, with the higher t mperatures merely reducing the reaction time. Howev r, excessively high temperatures are usually not preferr d so as to avoid unwanted secondary reactions.

The procedures for forming th instant peptides ar well known in this art and are provided in detail in th accompanying examples.

Since th selected tetrapyrrole contains more than one carboxyl group, mixtures of products can be formed in-including isomeric di- and even tri- or higher peptid products, depending on the number of carboxyl groups and depending on th selected stoichiometry. Thus, when equivalent mixtures of amino acid and tetrapyrrol ar r acted, the product may contain some monopeptid s, but also present will be di- or polypeptides. It is generally possible to separate the monopeptides and higher peptides using known chromatographic techniques. However, such separations are not necessary since the mixed peptides are usually comparable to the separated products in their ultimate use. Thus, mixtures of mono, di, and tri-peptides of the same tetrapyrrole can be used.

Usually, unreacted tetrapyrrole is separated from the peptide products of the invention during purification as, for example, by chromatographic techniques.

Photodiagnosis and Phototherapy

The compositions of the present invention are useful for the photodiagnosis and phototherapy of tumor, cancer and malignant tissue (hereinafter referred to as "tumor").

When a man or animal having tumor is treated with doses of a compound of the present invention and when appropriate light rays or electromagnetic waves are applied, the compound emits light, i.e., fluor s-cence. Thereby the existence, position and size of tumor can be detected, i.e., photo-diagnosis.

When the tumor is irradiated with light of proper wavelength and intensity, the compound is activated to exert a cell killing effect against the tumor. This is called "phototherapy".

Compounds intended for photodiagnosis and phototherapy ideally should have the following properties:

(a) non-toxic at normal therapeutic dosage unless and until activated by light;

(b) should be selectively photoactive;

(c) when light rays or electromagnetic waves are applied, they should emit characteristic and detectable fluorescence;

(d) when irradiated with light rays or electromagnetic waves are applied, they are activated to an extent to exert a cell killing effect against tumor; and

(e) easily metabolized or excreted after treatment.

In accordance with testing up to the present, the present new compounds have the foregoing properti s and are also characterized by reasonable solubility in saline at physiological pH.

The compounds in the present composition possess greater fluorescence in tumors than do th corresponding basic tetrapyrroles. Their use provides the best contrast in tumors compared to normal tissue around the tumor. The instant compounds absorb activating energy for phototherapy in the convenient range of 600 to 800 nanometers, with the preferred compounds absorbing in the 620-760 nanometer range, i.e., light of longer wavelengths which more readily permits penetration of energy into the tumor for phototherapeutic purpose.

In present experience, the present compounds more uniformly distribute throughout the tumor than th basic tetrapyrrole permitting the use of considerably lower dosage (to about 1/10th of the required normal dose of the basic tetrapyrrole) which lessens, if not eliminates, photosensitization in the host. They also possess a more consistent fluorescence whereas some of the corresponding tetrapyrroles show inconsistent fluorescence or the fluorescence varies from day to day in the host.

A particularly advantageous property of the present compounds resides in the ease with which they ar excreted by the host. Generally, within 48 to 72 hours of intravenous or intraperitoneal administration, there are little or no detectable amounts in normal muscle tissue. The present compounds which are excreted with their chromophore intact are recovered from the feces of the host within 48-72 hours of injection. Under equivalent circumstances, substantial amounts of the corresponding tetrapyrroles remain, as compared with only minor amounts of peptides formed with the aminocarboxylic acids remain in the host, e.g., up to about 20%. This property is extremely important in that it contributes to minimization of photosensitization of the host.

The instant compositions can be used for diagnosis and therapeutic treatment of a broad range of tumors. Examples of tumors are gastric cancer, enteric cancer, lung cancer, breast cancer, uterine cancer, esophageal cancer, ovarian cancer, pancreatic cancer, pharyngeal cancer, sarcomas, hepatic cancer, cancer of the urinary bladder, cancer of the upper jaw, cancer of the bile duct, cancer of the tongu , cerebral tumor, skin cancer, malignant goiter, prostatic cancer, cancer of the parotid gland, Hodgkins's disease, multiple myeloma, renal cancer, leukemia; and malignant lymphocytoma. For diagnosis, th sole requirement is that the tumor be capable of selectivity fluorescing when exposed to proper light. For treatment, th tumor must be penetrabl by the activation energy. For diagnosis, light of shorter wavelength is used whereas for therapeutic purposes light of longer wavelength is used to permit ready penetration of th

tumor tissue. Thus, for diagnosis, light of from 360 - 760 nanometers can be used, and for treatment, from 620 - 760, depending on the individual characteristics of the tetrapyrrole. The absorption characteristics of the present new compounds are substantially the same as the tetrapyrrole from which derived.

It is necessary that the light rays be so intense as to cause the compounds to emit fluorescence for diagnosis and to exert a cell killing effect for therapy.

The source of irradiation for photodiagnosis and phototherapy is not restricted, however, but the laser beam is preferable because intensive light rays in a desired wavelength range can be selectively applied. For example, in photodiagnosis, the compound of the invention is administered to a human or animal body, and after a certain period of time, light rays are applied to the part to be examined. When an endoscope can be used for the affected part, such as lungs, gullet, stomach, womb, urinary bladder or rectum, it is irradiated using the endoscope, and the tumor portion selectively emits fluorescence. This portion is observed visually, or observed through an adapted fiber scope by eye or on a CRT screen.

In phototherapy, after administration of the dosage, the irradiation is carried out by laser beams from the tip of quartz fibers. Besides the irradiation of the surface of tumor, the internal part of the tumor can be irradiated by inserting the tip of quartz fibers into the tumor. The irradiation can be visually observed or imaged on a CRT screen.

For photodiagnosis, light of wavelengths between 360 and 760 nm. is suitable for activating the present tetrapyrrole compounds. Of course, each compound has a specific optimal wavelength of activation. A long wavelength ultraviolet lamp is particularly suitable for photodiagnosis. Similar methods for viewing of the treated tumor can be used as already described for phototherapy.

The dosages of the present compositions will vary depending on the desired effect, whether for diagnosis or for treatment. For diagnosis, doses of as little as 1 mg /kg will be effective, and up to about 20 mg/kg can be used. For treatment, the dose will usually approximate about 0.5 mg/kg. Of course, the dosage for either diagnosis or treatment can be varied widely in view of aforesaid advantageous properties of the present compounds, e.g., the ease of elimination from the host, for one.

The present compositions are apparently non-toxic at the dosage levels employed for diagnosis or treatment. No mortality of test animals due the present compounds has been noted in studies employing dosage levels up to 20 mg/kg.

For both diagnosis and treatment, the present compositions can be administered by the oral, intravenous, or intramuscular routes. They can be formulated as lyophilized sterile, pyrogen-free compounds, preferably in the form of basic salts, e.g., sodium salt. The preferred dosage forms are provided as injectable solutions (isotonic).

The irradiation source used in treatment of tumors containing compounds of this invention is a filtered, high-intensity, continuous source or pumped dye, or other laser and light delivery system, which is capable of performing within the following limits: power intensity 20-500 mw/cm^2 at wavelengths between 620 and 700 nm. and a total output of at least 500 mw. or greater. Several currently commercially available lasers meet these criteria.

The tetrapyrroles can be prepared by various synthetic methods which are found in the literature, e.g.,

Pheophorbides

Willstatter, R., Stoll, A.; Investigations on Chlorophyll, (Transl. Schertz, FM.M., Merz, A.R.) p. 249. Science Printing Press, Lancaster, Pennsylvania, 1928.

Pennington, F.C. Strain, H.H., Svec, W.A., Katz, J.J.; J. Amer. Chem. Soc., 86, 1418 (1964).

Chlorin e_6

Willstatter, R. Stoll, A.; Investigations on Chlorophyll, (Trans., Schertz, F.M., Merz, A.R.,) p. 176. Science Printing Press, Lancaster, Pennsylvania, 1928.

Willstatter, R., Isler, M.; Ann. Chem., 390, 269 (1912).

Fisher, H., Baumler, P.; Ann Chem., 474, 65 (1929).

Fisher, H., Siebel, H.; Ann. Chem., 499, 84 (1932).

Conant, J.B., Mayer, W.W.; J. Amer. Chem. Soc., 52, 3013 (1930).

Chlorin e_4

Fisher, H., Heckmaier, J., Plotz, E.; Justus Leibigs Ann. Chem., 500, 215 (1933).

Chlorin e_6, e_4, isochlorin e_4.. mesochlorin e_6, bacteriopheophorbide, bacteriochlorin e_6

Fischer and Orth, "D s Chemie des Pyrrole" Akademisch Verlazsces llschaft, Leipzig, 1940, Vol. II, Part 2.

General Ref rence for Porphyrins

"Porphyrins and Metalloporphyrins" ed. Kevin M. Smith, Elsevier 1975 N.Y.

The compositions of the present invention can be administered to the host in a variety of forms adapted to the chosen route of administration, i.e., orally, intravenously, intramuscularly or subcutaneous routes.

The compositions may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shall gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the compositions may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elexirs, suspensions, syrups or wafers. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of the unit. Th amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, troches, pills or capsules may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch or alginic acid; a lubricant such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instanc , tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the compositions, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, th active compound may be incorporated into sustained-release preparations and formulations.

The composition may also be administered parenterally or intraperitoneally. Solutions of the composition as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol or liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid or thimerosal. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the composition in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from thos enumerated above. In the cas of steril powders for the preparation of sterile injectable solutions, th preferred methods of preparation are vacuum drying and the freez -drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously st rile-filtered solution th reof.

The present new compositions may also be applied directly to tumors, whether internal or external, in the host in topical compositions. Exemplary compositions include solutions of th new compounds in solvents, particularly aqueous solvents, most preferably water. Alternatively, for topical application particularly to skin tumors, the present new compounds may be dispersed in the usual cream or salve-formulations

commonly used for this purpose or may be provided in the form of spray solutions or suspensions which may includ a propellant usually employed in aerosol preparations.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents or isotonic and absorption delaying agents. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with th required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of tumors in living subjects.

The following examples further illustrate the invention.

Mono-, di and Triamides:

EXAMPLE 1

Di and mono(DL) serinyl mesoporphyrin IX (mixed anhydrides method)

400 mg (0.0007 moles) of mesoporphyrin IX were suspended in 50 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1 M KOH containing 761 mg (0.0072 moles) of DL serine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatrogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 liter total volume).

The column effluent was collected via fraction collector and the tube contents were pooled according to individual components. The order of elution was di-DL-serinyl mesoporphyrin IX, mono-DL-serinyl mesoporphyrin IX and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum. The yield of di (DL) serinyl mesoporphyrin IX was 95.6 mg.

EXAMPLE 2

Di and mono glycyl mesoporphyrin IX (mixed anhydride method)

100 mg (0.000175 moles) of mesoporphyrin IX were suspended in 100 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 500 mg (0.0066 moles) of glycine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0/13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of zero to 50% m thanol in 0.01 M KPO_4 buff r pH 6.85 (1 l total volume).

The column effluent was collected in a fraction collector and the contents wer sorted according to individual components. The order of elution was diglycyl mesoporphyrin IX, monoglycyl mesoporphyrin IX and unsubstitut d mesoporphyrin IX.

Th methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3

times with dilute acetic acid in water. The product was dried under vacuum.

EXAMPLE 3

Di and Mono α DL) alanyl mesoporphyrin IX (mixed anhydride method)

100 mg (0.000175 moles) of mesoporphyrin IX were suspended in 100 ml of tetrahydrofuran (THF). 210 µl (0.002 moles) of triethylamine were added with stirring. After 10 minutes 195 µl (0.00177 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 500 mg (0.0056 moles) of α (DL) alanine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volume).

The column effluent was collected via fraction collection and the tube contents were sorted according to individual components. The order of elution was di-α(DL) alanyl mesoporphyrin IX, mono- α(DL)-alanyl mesoporphyrin IX and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum.

EXAMPLE 4

Di and mono β alanyl mesoporphyrin IX (mixed anhydride method)

400 mg (0.0007 moles) of mesoporphyrin IX were suspended in 100 ml of tetrahydrafuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1 M KOH containing 400 mg (0.0044 moles) of β alanine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1,5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of 40-50% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volume).

The column effluent was collected via fraction collector and the tube contents were pooled according to individual components. The order of elution was di-β-alanyl mesoporphyrin IX, mono-β-alanyl mesoporphyrin IX, and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum. The yield for di-β-alanyl mesoporphyrin IX was 40 mg: the yield for mono-β-alanyl mesoporphyrin IX was 23 mg.

EXAMPLE 5

Di and mono ε amino-n-caproyl mesoporphyrin IX (mixed anhydride method)

400mg (0.0007 moles) of mesoporphyrin IX were suspended in 50 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 543 mg (0.00414 moles) of ε-amino-n-caproic acid were added to the THF solution. This mixture was stirred 60 minutes at room temperatur .

The organic solvent was flashed off and the r action mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5×30 cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volum).

The column efflu nt was collected via fraction collector and th tube contents were pooled according to

individual components. Th order of elution was di-ε-amino-n-caproyl mesoporphyrin IX, mono-ε-amino-n-caproyl mesoporphyrin IX, and unsubstitut d mesoporphyrin IX.

The methanol was flash d off and the material was precipitated at pH 2.5-3.0. Th ppt. was washed thre times with dilut acetic acid in water. The product was dried under vacuum. The yield of di-ε-amino-n-caproyl mesoporphyrin IX was 237 mg.

EXAMPLE 6

Di and mono-β-alanyl hematoporphyrin IX (mixed anhydride method)

400 mg (0.00059 moles of hematoporphyrin IX dihydrochloride were suspended in 50 ml of tetrahydrofuran (THF).

360µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340µl (0.0031 moles) of ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 400 mg (0.0044 moles) of β alanine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was removed by flash evaportaion, keeping the temperature below 50°C. The reaction mixture was checked for product by silica TLC using Benzene/methanol/88% formic acid (8.5/1.5/0.13) as solvent to develop the chromatogram.

The solution was adjusted to pH 7.5-8.0 with HCl and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The mixture was resolved using a linear gradient of 40-80% methanol in 0.01M KPO_4 buffer pH 6.85 (1 liter total volume). The individual components were collected as they came off the column in the order di-β-alanyl hematoporphyrin IX, mono-β-alanyl hematoporphyrin IX and hematoporphyrin IX.

The methanol was removed from each component by flash evaporation and the material was precipitated by adjusting the pH to 2.5 - 3.0 using HCl. The precipitate was washed three times with dilute acetic acid in water at the centrifuge and the products dried under vacuum. The yield of di-β-alanyl hematoporphyrin IX was 52mg and of mono-β-alanyl hematoporphyrin was 30 mg.

EXAMPLE 7

Di-L-α-Serinyl chlorin e_6 (mixed anhydride method)

650 mg of chlorin e_6 were dissolved in 30 ml of dimethylformide (DMF). 227 µl (0.002 moles) of triethylamine were added to the DMF solution. After stirring for five minutes, 201 µl (0.002 moles) of ethyl chloroformate were added and stirring was continued for an additional 30 minutes. 0.95 g (0.009 moles) of L-α-serine were added to the DMF solution and allowed to stir for one hour at 50-60°C.

The DMF solution was checked for product formation by reverse phase (C-18 silica) TLC using methanol/0.01 M sodium phosphate buffer, pH 6.85, (7.0/3.0) to develop the chromatogram. The DMF solution was flash evaporated to near dryness and the reaction mixture was then taken up in dilute NaOH and the pH was adjusted to 2.5-3.0 to precipitate out the mixture. The precipitate was then centrifuged down and washed twice with diluted acetic acid in water. The precipitate was then centrifuged down and washed twice with diluted acetic acid in water. The precipitate was then redissolved in dilute NaOH and th pH adjusted to 7.0. This was applied to a reverse phase (C-18 silica) column 3.7 cm x 45 cm.

The product was eluted from the column with a solution of 0.01.M sodium phosphate buffer, pH 6.85/methanol (7.0/3.0). Fractions were collected and the fractions of pure di-L-α-serinyl chlorin e_6 wer pooled. The methanol was flashed off and the product was precipitated at pH 2.5-3.0. The precipitate was centrifuged down, washed three times with dilute acetic acid, and dried under vacuum. The yield was 200 mg of di-L-α-serinyl chlorin e_6.

Utilizing the aforementiond carbodiimide or th mixed anhydride methods, the following preferred compounds of this invention can be synthesized:

Chlorin Derivatives

Di - (DL)-serinyl-trans-mesochlorin IX
Di - glycyl-trans-mesochlorin IX

Di -α-(DL)-alanyl-trans-mesochlorin IX
Di -β-alanyl-trans-m sochlorin IX
Di -ε-amino-n-caproyl-mesochlorin IX
Di, tri- (D,L)-serinyl chlorin e_6
Di, tri- (D,L)-serinyl mesochlorin e_6
Di, tri- glycyl chlorin e_6
Di, tri- glycyl mesochlorin e_6
Di, tri-α-(D,L)-alanyl chlorin e_6
Di, tri-α-(D,L)-alanyl mesochlorin e_6
Di, tri-β-alanyl chlorin e_6
Di, tri-β-alanyl mesochlorin e_6
Di, tri-ε-amino-n-caproyl chlorin e_6
Di, tri-ε-amino-n-caproyl mesochlorin e_6
Di- (D,L)-serinyl chlorin e_4
Di- (D,L)-serinyl mesochlorin e_4
Di- (D,L)-serinyl isochlorin e_4
Di- (D,L)-serinyl mesoisochlorin e_4
Di- glycyl chlorin e_4
Di- glycyl mesochlorin e_4
Di- glycyl isochlorin e_4
Di- glycyl mesoisochlorin e_4
Di-α-(DL)-alanyl chlorin e_4
Di-α-(DL)-alanyl mesochlorin e_4
Di-α-(DL)-alanyl isochlorin e_4
Di-α-(DL)-alanyl mesoisochlorin e_4
Di-β-alanyl chlorin e_4
Di-β-alanyl mesochlorin e_4
Di-β-alanyl isochlorin e_4
Di-β-alanyl mesoisochlorin e_4
Di-ε-amino-n-caproyl chlorin e_4
Di-ε-amino-n-caproyl mesochlorin e_4
Di-ε-amino-n-caproyl isochlorin e_4
Di-ε-amino-n-caproyl mesoisochlorin e_4
Di- (D,L)-serinylphotoprotoporphyrin IX
Di- glycylphotoprotoporphyrin IX
Di-α-(D,L)-alanylphotoprotoporphyrin IX
Di-β-alanylphotoprotoporphyrin IX
Di-ε-amino-n-caproylphotoprotoporphyrin IX

Porphyrin Derivatives

Di- (D,L)-serinylmesoporphyrin IX
Di- glycylmesoporphyrin IX
Di-α-(DL)-alanylmesoporphyrin IX
Di-β-alanylmesoporphyrin IX
Di-ε-amino-n-caproylmesoporphyrin IX
Di-(D,L)-serinylprotoporphyrin IX
Di-glycylprotoporphyrin IX
Di-α-(D,L)-alanylprotoporphyrin IX
Di-β-alanylprotoporphyrin IX
Di-ε-amino-n-caproylprotoporphyrin IX
Di-(D,L)-s rinyldeuteroporphyrin IX
Di-glycyldeuteroporphyrin IX
Di-α-(D,L)-alanyldeuteroporphyrin IX
Di-β-alanyldeuteroporphyrin IX
Di-ε-amino-n-caproyld uteroporphyrin IX
Di, tri, tetra- (D,L)-serinylcoproporphyin III
Di, tri, tetra- glycylcoproporphyrin III

Di, tri, tetra-α-(D,L)-alanylcoproporphyrin III
Di, tri, tetra-β-alanylcoproporphyrin III
Di, tri, tetra-ε-amino-n-caproylcoproporphyrin III
Di-(D,L)-serinylhematoporphyrin IX
Di-glycylhematoporphyrin IX
Di-α-(D,L)-alanylhematoporphyrin IX
Di-β-alanylhematoporphyrin IX
Di-ε-amino-n-caproylhematoporphyrin IX

Bacteriochlorin Derivatives

Di-(D,L)-serinylbacteriochlorin e_4
Di-glycylbacteriochlorin e_4
Di-α-(DL)-alanylbacteriochlorin e_4
Di-β-alanylbacteriochlorin e_4
Di-ε-amino-n-caproylbacteriochlorin e_4
Di-(D,L)-serinylbacterioisochlorin e_4
Di-glycylbacterioisochlorin e_4
Di-α-(D,L)-alanylbacterioisochlorin e_4
Di-β-alanylbacterioisochlorin e_4
Di-ε-amino-n-caproylbacterioisochlorin e_4
Di, tri- (D,L)-serinylbacteriochlorin e_6
Di, tri- glycylbacteriochlorin e_6
Di, tri-α-(D,L)-alanylbacteriochlorin e_6
Di, tri-β-alanylbacteriochlorin e_6
Di, tri-ε-amino-n-caproylbacteriochlorin e_6

Similarly, by utilizing other amino acids, peptides which further illustrate embodiments of, but do not limit the present invention, can be employed:

Di-threoninyl trans-mesochlorin IX
Di,tri-threoninyl chlorin e_6
Di,tri-threoninyl mesochlorin e_6
Di-threoninyl chlorin e_4
Di-threoninyl mesochlorin e_4
Di-threoninyl isochlorin e_4
Di-threoninyl mesoisochlorin e_4
Di-threoninyl photoprotoporphyrin IX
Di-threoninyl mesoporphyrin IX
Di-threoninyl protoporphyrin IX
Di-threoninyl deuteroporphyrin IX
Di,tri,tetra-threoninyl coproporphyrin III
Di-threoninyl hematoporphyrin IX
Di-threoninyl bacteriochlorin e_4
Di-threoninyl bacterioisochlorin e_4
Di,tri-threoninyl bacteriochlorin e_6
Di-cysteinyl trans-mesochlorin IX
Di,tri-cysteinyl chlorin e_6
Di,tri-cysteinyl mesochlorin e_6
Di-cysteinyl chlorin e_4
Di-cysteinyl isochlorin e_4
Di-cysteinyl mesoisochlorin e_4
Di-cysteinyl photoprotoporphyrin IX
Di-cysteinyl mesoporphyrin IX
Di-cysteinyl protoporphyrin IX
Di-cysteinyl deuteroporphyrin IX
Di,tri,tetra-cysteinyl-coproporphyrin III
Di-cysteinyl hematoporphyrin IX
Di-cysteinyl bacteriochlorin e_4
Di-cysteinyl bacterioisochlorin e_4

Di, tri-cysteinyl bacteriochlorin e_6
Di-tyrosyl trans-mesochlorin IX
Di, tri-tyrosyl chlorin e_6
Di,tri-tyrosyl mesochlorin e_6
Di-tyrosyl chlorin e_4
Di-tyrosyl mesochlorin e_4
Di-tyrosyl isochlorin e_4
Di-tyrosyl mesoisochlorin e_4
Di-tyrosyl photoprotoporphryin IX
Di-tyrosyl mesoporphyrin IX
Di-tyrosyl protoporphyrin IX
Di-tyrosyl deuteroporphyrin IX
Di,tri,tetra-tyrosyl coproporphyrin III
Di-tyrosyl hematoporphryin IX
Di-tyrosyl bacteriochlorin e_4
Di-tyrosyl bacterioisochlorin e_4
Di,tri-tyrosyl bacteriochlorin e_6
Di-valyl trans-mesochlorin IX
Di,tri-valyl chlorin e_6
Di,tri-valyl mesochlorin e_6
Di-valyl chlorin e_4
Di-valyl mesochlorin e_4
Di-valyl isochlorin e_4
Di-valyl mesoisochlorin e_4
Di-valyl photoprotoporphyrin IX
Di-valyl mesoporphyrin IX
Di-valyl protoporphyrin IX
Di-valyl deuteroporphyrin IX
Di,tri,tetra-valyl coproporphyrin III
Di-valyl hematoporphyrin IX
Di-valyl bacteriochlorin e_4
Di-valyl bacterioisochlorin e_4
Di,tri-valyl bacteriochlorin e_6
Di-leucyl trans-mesochlorin IX
Di,tri-leucyl chlorin e_6
Di,tri-leucyl mesochlorin e_6
Di-leucyl chlorin e_4
Di-leucyl mesochlorin e_4
Di-leucyl isochlorin e_4
Di-leucyl mesoisochlorin e_4
Di-leucyl photoprotoporphyrin IX
Di-leucyl mesoporphyrin IX
Di-leucyl protoporphyrin IX
Di-leucyl deuteroporphyrin IX
Di,tri,tetra-leucyl coproporphyrin III
Di-leucyl hematoporphyrin IX
Di-leucyl bacteriochlorin e_4
Di-leucyl bacterioisochlorin e_4
Di,tri-leucyl bacteriochlorin e_6
Di-isoleucyl trans-mesochlorin IX
Di,tri-isoleucyl chlorin e_6
Di,tri-isoleucyl mesochlorin e_6
Di-isoleucyl chlorin e_4
Di-isoleucyl mesochlorin e_4
Di-isoleucyl isochlorin e_4
Di-isoleucyl mesoisochlorin e_4
Di-isoleucyl photoprotoporphyrin IX
Di-isoleucyl mesoporphyrin IX

Di-isoleucyl protoporphyrin IX
Di-isoleucyl deuteroporphyrin IX
Di,tri,t tra-isoleucyl coproporphyrin III
Di-isoleucyl hematoporphyrin IX
Di-isoleucyl bacteriochlorin e_4
Di-isoleucyl bacterioisochlorin e_4
Di,tri-isoleucyl bacteriochlorin e_6
Di-prolyl trans-mesochlorin IX
Di,tri-prolyl chlorin e_6
Di,tri-prolyl mesochlorin e_6
Di-prolyl chlorin e_4
Di-prolyl mesochlorin e_4
Di-prolyl isochlorin e_4
Di-prolyl mesoisochlorin e_4
Di-prolyl photoprotoporphyrin IX
Di-prolyl mesoporphryin IX
Di-prolyl protoporphyrin IX
Di-prolyl deuteroporphyrin IX
Di,tri,tetra-prolyl coproporphyrin III
Di-prolyl hematoporphyrin IX
Di-prolyl bacteriochlorin e_4
Di-prolyl bacteriiosochlorin e_4
Di,tri-prolyl bacteriochlorin e_6
Di-phenylalanyl trans-mesochlorin IX
Di,tri-phenylalanyl chlorin e_6
Di,tri-phenylalanyl mesochlorin e_6
Di-phenylalanyl chlorin e_4
Di-phenylalanyl mesochlorin e_4
Di-phenylalanyl isochlorin e_4
Di-phenylalanyl mesoisochlorin e_4
Di-phenylalanyl photoprotoporphyrin IX
Di-phenylalanyl mesoporphyrin IX
Di-phenylalanyl protoporphyrin IX
Di-phenylalanyl deuteroporphyrin IX
Di,tri,tetra-phenylalanyl coproporphyrin III
Di-phenylalanyl hematoporphyrin IX
Di-phenylalanyl bacteriochlorin e_4
Di-phenylalanyl bacterioisochlorin e_4
Di,tri-phenylalanyl bacteriochlorin e_6
Di-tryptophyl trans-mesochlorin IX
Di,tri-tryptophyl chlorin e_6
Di,tri-tryptophyl mesochlorin e_6
Di-tryptophyl chlorin e_4
Di-tryptophyl mesochlorin e_4
Di-tryptophyl isochlorin e_4
Di-tryptophyl mesoisochlorin e_4
Di-tryptophyl photoprotoporphyrin IX
Di-tryptophyl mesoporphyrin IX
Di-tryptophyl protoporphyrin IX
Di-tryptophyl deuteroporphyrin IX
Di,tri,tetra-tryptophyl coproporphyrin III
Di-tryptophyl hematoporphyrin IX
Di-tryptophyl bacteriochlorin e_4
Di-tryptophyl bacterioisochlorin e_4
Di,tri-tryptophyl bacteriochlorin e_6
Di-methionyl trans-mesochlorin IX
Di,tri-methionyl chlorin e_6
Di,tri-methionyl mesochlorin e_6

Di-methionyl chlorin e_4
Di-methionyl mesochlorin e_4
Di-methionyl isochlorin e_4
Di-methionyl mesoisochlorin e_4
Di-methionyl photoprotoporphyrin IX
Di-methionyl mesoporphyrin IX
Di-methionyl protoporphyrin IX
Di-methionyl deuteroporphyrin IX
Di,tri,tetra-methionyl coproporphyrin III
Di-methionyl hematoporphyrin IX
Di-methionyl bacteriochlorin e_4
Di-methionyl bacterioisochlorin e_4
Di,tri-methionyl bacteriochlorin e_6
Di-histidyl trans-mesochlorin IX
Di,tri-histidyl Chlorin e_6
Di,tri-histidyl mesochlorin e_6
Di-histidyl chlorin e_4
Di-histidyl mesochlorin e_4
Di-histidyl isochlorin e_4
Di-histidyl mesoisochlorin e_4
Di-histidyl photoprotoporphyrin IX
Di-histidyl mesoporphyrin IX
Di-histidyl protoporphyrin IX
Di-histidyl deuteroporphyrin IX
Di tri,tetra-histidyl coproporphyrin III
Di-histidyl hematoporphyrin IX
Di-histidyl bacteriochlorin e_4
Di-histidyl bacterioisochlorin e_4
Di,tri-histidyl bacteriochlorin e_6
Di-arginyl trans-mesochlorin IX
Di,tri-arginyl chlorin e_6
Di,tri-arginyl mesochlorin e_6
Di-arginyl chlorin e_4
Di-arginyl mesochlorin e_4
Di-arginyl isochlorin e_4
Di-arginyl mesoisochlorin e_4
Di-arginyl photoprotoporphyrin IX
Di-arginyl mesoporphryin IX
Di-arginyl protoporphyrin IX
Di-arginyl deuteroporphyrin IX
Di,tri,tetra-arginyl coproporphyrin III
Di-arginyl hematoporphyrin IX
Di-arginyl bacteriochlorin e_4
Di-arginyl bacterioisochlorin e_4
Di,tri-arginyl bacteriochlorin e_6
Di-lysyl trans-mesochlorin IX
Di,tri-lysyl chlorin e_6
Di,tri-lysyl mesochlorin e_6
Di-lysyl chlorin e_4
Di-lysyl mesochlorin e_4
Di-lysyl isochlorin e_4
Di-lysyl mesoisochlorin e_4
Di-lysyl photoprotoporphyrin IX
Di-lysyl mesoporphyrin IX
Di-lysyl protoporphyrin IX
Di-lysyl deuteroporphyrin IX
Di,tri,tetra-lysyl coproporphyrin III
Di-lysyl hematoporphyrin IX

Di-lysyl bacteriochlorin e_4
Di-lysyl bacterioisochlorin e_4
Di,tri-lysyl bacteriochlorin e_5
Di-glutaminyl trans-m sochlorin IX
Di,tri-glutaminyl chlorin e_5
Di,tri-glutaminyl mesochlorin e_5
Di-glutaminyl chlorin e_4
Di-glutaminyl mesochlorin e_4
Di-glutaminyl isochlorin e_4
Di-glutaminyl mesoisochlorin e_4
Di-glutaminyl photoprotoporphyrin IX
Di-glutaminyl mesoporphyrin IX
Di-glutaminyl protoporphyrin IX
Di-glutaminyl deuteroporphyrin IX
Di,tri,tetra-glutaminyl coproporphyrin III
Di-glutaminyl hematoporphyrin IX
Di-glutaminyl bacteriochlorin e_4
Di-glutaminyl bacterioisochlorin e_4
Di,tri-glutaminyl bacteriochlorin e_5
Di-asparginyl trans-mesochlorin IX
Di,tri-asparginyl chlorin e_5
Di,tri-asparginyl mesochlorin e_5
Di-asparginyl chlorin e_4
Di-asparginyl mesochlorin e_4
Di-asparginyl isochlorin e_4
Di-asparginyl mesoisochlorin e_4
Di-asparginyl photoprotoporphyrin IX
Di-asparginyl mesoporphyrin IX
Di-asparginyl protoporphyrin IX
Di-asparginyl deuteroporphyrin IX
Di,tri,tetra-asparginyl coproporphyrin III
Di-asparginyl hematoporphyrin IX
Di-asparginyl bacteriochlorin e_4
Di-asparginyl bacterioisochlorin e_4
Di,tri-asparginyl bacteriochlorin e_5

Monoamides

EXAMPLE 8

Mono (DL) serinyl mesoporphyrin IX (mixed anhydride method)

400 mg (0.0007 moles) of mesoporphyrin IX were suspended in 50 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1 M KOH containing 761 mg (0.0072 moles) of DL serine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatrogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 liter total volume).

Th column effluent was collected via fraction collector and the tube contents were pooled according to individual components. The order of elution was diserinyl mesoporphyrin IX, monoserinyl mesoporphyrin IX and unsubstituted mesoporphyrin IX.

Th methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum.

Example 9

Mono glycyl mesoporphyrin IX (mixed anhydride method)

100 mg (0.000175 moles) of m soporphyrin IX wer suspended in 100 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 500 mg (0.0066 moles) of glycine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0/13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of zero to 50% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volume).

The column effluent was collected in a fraction co-lector and the contents were sorted according to individual components. The order of elution was diglycyl mesoporphyrin IX, monoglycyl mesoporphyrin IX and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum.

EXAMPLE 10

Mono α (DL) alanyl mesoporphyrin IX (Mixed anhydride method)

100 mg (0.000175 moles) of mesoporphyrin IX were suspended in 100 ml of tetrahydrofuran (THF). 210 µl (0.002 moles) of triethylamine were added with stirring. After 10 minutes 195 µl (0.00177 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 500 mg (0.0056 moles) of α(DL) alanine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volume).

The column effluent was collected via fraction collection and the tube contents were sorted according to individual components. The order of elution was di-α(DL) alanyl mesoporphyrin IX, mono- α(DL)-alanyl mesoporphyrin IX and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3 times with dilute acetic acid in water. The product was dried under vacuum.

EXAMPLE 11

Mono β alanyl mesoporphyrin IX (mixed anhydride method)

400 mg (0.0007 moles) of mesoporphyrin IX were suspended in 100 ml of tetrahydrafuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01) moles) of 1 M KOH containing 400 mg (0.0044 moles) of β alanine were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1,5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5 x 30 cm. The r action mixture was resolved using a linear gradient of 40-80% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volum).

Th column effluent was collected via fraction collector and the tub contents were pooled according to individual components. The order of elution was di-β-alanyl mesoporphyrin IX, mono-β-alanyl mesoporphyrin IX, and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed 3

times with dilute acetic acid in water. The product was dried under vacuum. Th yi ld for mono-β-alanyl mesoporphyrin IX was 23 mg.

EXAMPLE 12

Mono ε amino-n-caproyl mesoporphyrin IX (mixed anhydride method,

400mg (0.0007 moles) of mesoporphyrin IX were suspended in 50 ml of tetrahydrofuran (THF). 360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.00414 moles) of ethylchloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 543 mg (0.00369 moles) of ε-amino-n-caproic acid were added to the THF solution. This mixture was stirred 60 minutes at room temperature.

The organic solvent was flashed off and the reaction mixture was checked by silica TLC for product. Benzene/methanol/88% formic acid (8.5/1.5/0.13) was used to develop the chromatogram.

After checking for product, the solution was adjusted to pH 7.5-8.0 and placed on a reverse phase (C-18 silica) column 2.5×30cm. The reaction mixture was resolved using a linear gradient of 20-70% methanol in 0.01 M KPO_4 buffer pH 6.85 (1 ℓ total volume).

The column effluent was collected via fraction collector and the tube contents were pooled according to individual components. The order of elution was di-ε-amino-n-caproyl mesoporphyrin IX, mono-ε-amino-n-caproyl mesoporphyrin IX, and unsubstituted mesoporphyrin IX.

The methanol was flashed off and the material was precipitated at pH 2.5-3.0. The ppt. was washed three times with dilute acetic acid in water. The product was dried under vacuum.

EXAMPLE 13

Mono -β-alanyl hematoporphyrin IX (mixed anydride method)

400 mg (0.00059 moles) of hematoporphyrin IX dihydrochloride were suspended in 50 ml of tetrahydrofuran (THF).

360 µl (0.0035 moles) of triethylamine were added with stirring. After 10 minutes, 340 µl (0.0031 moles) of ethyl chloroformate were added. After stirring 10 minutes, 10 ml (0.01 moles) of 1M KOH containing 400 mg (0.0044 moles) of β-alanine were added to the THF solution. This mixture gas stirred 60 minut s at room temperature.

The organic solvent was removed by flash evaporation, keeping the temperature below 50°C. Th reaction mixture was checked for product by silica TLC using Benzene/methanol 88% formic acid (8.5/1.5/0.13) as solvent to develop the chromatogram.

The solution was adjusted to pH 7.5-8.0 with HCl and placed on reverse phase (C-18 silica) column 2.5 × 30 cm. The mixture was resolved using a linear gradient of 40-80% methanol in 0.01 M KPO_4 buffer pH 6.65 (1 liter total volume). The individual components were collected as they came off the column in th order di-β alanyl hematoporphyrin IX, mono -β- alanyl hematoporphyrin IX and hematoporphyrin IX.

The methanol was removed from each component by flash evaporation and the material was precipitated by adjusting the pH to 2.5 -3.0 using HCl. The precipitate was washed three times with dilute acetic acid in water at the centrifuge and the products dried under vacuum. The yield of di-β- alanyl hematoporphyrin IX was 52mg and of mono - β-alanyl hematoporphyrin was 30 mg.

EXAMPLE 14

Mono glycyl chlorin e_6 (Mixed Anhydride Method)

625 mg of chlorin e_6 were dissolved in 300 ml of dimethyl formamide (DMF) and 277 µl (0.002 mol s) of triethylamine (TEA) were added to the DMF solution. After stirring for five minutes, 201 µl (0.002 moles) of ethylchloroformate (EC) wer added and stirred for 1 1/2 hours at room temperatur .

75 mg (.0009 moles) of glycin (ammonia free) were added to the DMF solution and allowed to stir three hours at 50-60°C.

The DMF solution was tested for product by reverse phase (C-18 silica) TLC using methanol/0.01M sodium phosphate buffer, pH 6.85, 70/30, to develop the chromatogram.

The DMF solution was flashed to near dryness, then dissolved in dilute NaOH and the pH adjusted to 2.5-3 to precipitate th solid. The precipitate was then placed on a reverse phase (C-18 silica) column 3.7

cm x 45 cm.

Fractions were eluted, using 20-40% methanol in 0.01 M sodium phosphate buffer, pH 6.85. The fractions wer pooled according to individual components.

The m thanol was flashed off and the mat rial was precipitated at pH 2.5-3.0. The precipitate was washed and centrifuged 3 times in dilute acetic acid in water. The product was dried under vacuum. The yield of mono glycyl chlorin e_6 was 87.5 mg.

EXAMPLE XV

Preparation of mono-L-serinyl chlorin e_6

Chlorin e_6 was prepared according to the procedure of Fischer and Stern, Die Chemie Des Pyrroles, Volume II, second half, Leipzig 1940, Akademische Verlagsgesellschaft, pp. 91-93.

100 mg of the chlorin e_6 (free acid form) and 35 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were dissolved in 2 ml of N, N'-dimethyl formamide. After 5 minutes, 125 mg of L-serin benzyl ester hydrochloride was added, stirred vigorously until solution was complete, then allowed to stand at room temperature for 2 hours. At this time 0.5 ml of glacial acetic acid were added, then 30 ml of methanol and 12 ml of H_2O.

The solution was applied to a C-18 reverse phase column (14 x 2 cm). The column was washed with H_2O (100 ml) then 4 ml of 1M NH_4OH, then with H_2O again (50 ml). Eluted product with MeOH/H_2O. Fractions eluted from the column with 30% to 80% MeOH contained product as well as carbodiimid activated chlorin as determined by TLC on C-18 reverse phase plates with solvent 70% MeOH/30% buffer (0.1M sodium phosphate pH 6.85) V/V.

These fractions were pooled and enough 3 N NaOH was added to make the solution 0.1N in NaOH. After 1 hour, the hydrolysis was complete as determined by TLC in the above system. Removed the methanol by rotary evaporation and adjusted the pH of the solution to 7.5 with HCl. The chlorin solution was then reapplied to the same reverse phase column, washed with water, and eluted with MeOH/water using a stepwise gradient from 10 to 50% methanol. The fractions containing pure mono-L-serinyl chlorin as determined by TLC (R_f slightly greater than the unsubstituted chlorin) were pooled, the methanol removed by rotary evaporation, and the product dried as the trisodium salt by lyophylization.

EXAMPLE XVI

Preparation of mono-L-asparaginyl chlorin e_6

500 mg of chlorin e_6 and 175 mg of 1-ethyl-3-(3-dimethylamine-propyl) carbodiimide hydrochloride were dissolved in 10 ml of N, N'-dimethyl formamide. After 5 minutes, 410 mg of L-asparagine were added. The solution was agitated for 4 hours. The asparagine did not dissolve totally during this reaction, but reverse phase (C-18) TLC 70/30 MeOH/.01M sodium phosphate buffer pH 6.85 showed some product at this time, (R_f slightly greater than chlorin e_6). The reaction was terminated by adding 2.5 ml glacial acetic acid, then diluting to a total volume of 100 ml with methanol, then adding 25 ml of H_2O slowly, with stirring. The solution was then applied to a 14 x 2 cm reverse phase (C-18) column, washed with water then with 5 ml of 0.1M NaOH, finally with 50 ml of 0.01 M sodium phosphate buffer, pH 6.85. The product was eluted off with MeOH/H_2O in a stepwise gradient from 20% MeOH to 50% MeOH. The fractions containing pure mono-L-asparaginyl chlorin e_6, as determined by TLC using the conditions stated above, were pooled, and the methanol removed by rotary evaporation. The product was isolated as the trisodium salt by lyophlization.

EXAMPLE XVII

Preparation of mono-L-cysteinyl chlorin e_6

300 mg of chlorin e_6 and 105 mg of 1-ethyl-3-(3-dimethylamine-propyl)carbodiimide hydrochloride were dissolved in 6 ml of N, N'-dimethylformamid . After 5 minutes, 255 mg of L-cysteine hydrochloride were added. The solution was stirred at room temperature for 5 hours. The rest of the procedure is the sam as for the preparation of mono-L-asparaginyl chlorin e_6.

EXAMPLE XVIII

Preparation of mono-L-serinyl-2- formylchlorin e_6 (mono-L-s rinyl 2-desvinyl-2-formyl-chlorin e_6)

500 mg of chlorin e_6 trimethyl ester were prepared according to the procedure of Fischer and Stern, in Die Chemie Des Pyrroles, Volume II, second half, Leipzig 1940, Akademische Verlagsgesellschaft, pp. 98-102. The chlorin e_6 trimethyl ester was dissoved in 600 ml of refluxing acetone. 400 mg of Potassium permanganate and 800 mg of magnesium sulfate dissolved in 130 ml of H_2O were added slowly over approximately a one hour period to the reluxing acetone solution. The solution was allowed to reflux for 1/2 hour after addition was complete. After cooling, 300 ml of methylene chloride were added, and the mixture was washed 3 times with water in a separatory funnel. The volume of methylene chloride was reduced and the product chromatographed on silica gel, eluting with a gradually increasing percentage of ethyl acetate in the CH_2Cl_2. The first major brown band which eluted was collected as the product, 2-Desvinyl-2-Formyl-Chlorin e_6. Yield 94 mg.

The product was saponified by dissolution in refluxing n-propanol (0.1 ml/mg) and addition of 6 fold equivalent of 1N KOH. The tripotassium salt was filtered off, washed with n-propanol and dried under vacuum, forming 2-formyl chlorin e_6.

100 mg of the 2-formyl chlorin e_6 free acid form) and 35 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were dissolved in 2 ml of N, N'-dimethyl formamide. After 5 minutes, 125 mg of L-serine benzyl ester hydrochloride was added, stirred vigorously until solution was complete, then allowed to stand at room stemperature for 2 hours. At this time 0.5 ml of glacial acetic acid was added, then 30 ml of methanol and 12 ml of H_2O.

The solution was applied to a C-18 reverse phase column (14 x 2 cm). The column was washed with H_2O (100 ml) then 4 ml of 1M NH_4OH, then with H_2O again (50 ml). Eluted product with MeOH/H_2O. Fractions eluted from the column with 30% to 80% MeOH contained product as well as carbodiimid activated chlorin as determined by TLC on C-18 reverse phase plates with solvent 70% MeOH/30% buffer (0.1M sodium phosphate pH 6.85) V/V.

These fractions were pooled and enough 3 N NaOH was added to make the solution 0.1N in NaOH. After 1 hour, the hydrolysis was complete as determined by TLC in the above system. Removed th methanol by rotary evaporation and adjusted the pH of the solution to 7.5 with HCl. The chlorin solution was then reapplied to the same reverse phase column, washed with water, and eluted with MeOH/water using a stepwise gradient from 10 to 50% methanol. The fractions containing pure mono-L-serinyl chlorin as determined by TLC (R_f slightly greater than the unsubstituted chlorin) were pooled, the methanol removed by rotary evaporation, and the product dried as the trisodium salt by lyophylization.

EXAMPLE XIX

Preparation of mono-L-serinyl-deuterochlorin e_6 (Mono-L-Serinyl 2-desvinyl-chlorin e_6)

A. Deuterochlorin e_6

Deuterchlorin e_6 trimethyl ester was prepared according to the procedure in Fischer and Stern in Di Chemie Des Pyrroles, Volume II, second half, Leipzig 1940, Akademische Verlagsgesellschaft, p. 104.
The trimethyl ester was then hydrolyzed to the free acid state by dissolution in refluxing n-propanol (0.1 ml/mg) and adding 6 fold equivalent amounts of 1N KOH. The product was collected by filtration, aft r cooling, as the potassium salt and dried under vaccum.

B. Mono-L-Serinyl Deuterochlorin e_6

100 mg of the deuterchlorin e_6 (free acid form) and 35 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were dissolved in 2 ml of N, N' dimethyl formamide. After 5 minutes, 125 mg of L-serine benzyl ester hydrochloride were added, stirred vigorously until solution was complete, then allowed to stand at room temperature for 2 hours. At this time 0.5 ml of glacial acetic acid were added, then 30 ml of methanol and 12 ml of H_2O.

The solution was applied to a C-18 r verse phase column (14 x 2 cm). The column was washed with H_2O (100 ml) then 4 ml of 1M NH_4OH, then with H_2O again (50 ml). Eluted product with MeOH/H_2O. Fractions eluted from the column with 30% to 80% MeOH contained product as well as carbodiimide activated chlorin as determined by TLC on C-18 reverse phase plates with solvent 70% MeOH/30% buff r (0.1M sodium phosphate pH 6.85) V/V.

Thes fractions were pooled and enough 3 N NaOH was added to make the solution 0.1N in NaOH.

After 1 hour, th hydrolysis was complete as determined by TLC in the above system. Remov d the methanol by rotary vaporation and adjusted the pH of the solution to 7.5 with HCl. The chlorin solution was then reappli d to th sam reverse phas column, washed with water, and eluted with MeOH/water using a stepwise gradient from 10 to 50% methanol. The fractions containing pure mono-L-serinyl chlorin, as determined by TLC (R_f slightly greater than the unsubstituted chlorin) were pooled, the methanol removed by rotary evaporation, and the product dried as the trisodium salt by lyophylization.

EXAMPLE XX

Preparation of mono-L-serinyl-2 acetyl-chlorin e_6 (Mono-L-serinyl-2-desvinyl-2-acetyl chlorin e_6)

A. 2-acetyl chlorin e_6

2-acetyl chlorin e_6 trimethyl ester was prepared according to the procedure of Fischer and Stern, Die Chemie Des Pyrroles, Volume II, second half, Leipzig 1940, Akademische Verlagsgesellschaft, p. 185. The trimethyl ester was then hydrolyzed to the free acid state by dissolution in refluxing n-propanol (0.1 ml/mg) and adding 6 fold equivalent amounts of 1N KOH. The product was collected by filtration, after cooling, as the potassium salt and dried under vaccum.

B. L-serinyl-2-acetyl chlorin e_6

100 mg of the 2-acetyl chlorin e_6 (free acid form) and 35 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were dissolved in 2 ml of N, N'-dimethyl formamide. After 5 minutes, 125 mg of L-serine benzyl ester hydrochloride were added, stirred vigorously until solution was complete, then allow d to stand at room temperature for 2 hours. At this time 0.5 ml of glacial acetic acid were added, then 30 ml of methanol and 12 ml of H_2O.

The solution was applied to a C-18 reverse phase column (14 x 2 cm). The column was washed with H_2O (100 ml) then 4 ml of 1M NH_4OH, then with H_2O again (50 ml). Eluted product with MeOH/H_2O. Fractions eluted from the column with 30% to 80% MeOH contained product as well as carbodiimide activated chlorin as determined by TLC on C-18 reverse plates with solvent 70% MeOH/30% buffer (.01M sodium phosphate, pH 6.85) V/V.

These fractions were pooled and enough 3N NaOH was added to make the solution 0.1N in NaOH. After 1 hour, the hydrolysis was complete as determined by TLC in the above system. Removed the methanol by rotary evaporation and adjusted the pH of the solution to 7.5 with HCl. The chlorin solution was then reapplied to the same reverse phase column, washed with water, and eluted with MeOH/water using a stepwise gradient from 10 to 50% methanol. The fractions containing pure mono-L-serinyl chlorin as determined by TLC (R_f slightly greater than the unsubstituted chlorin) were pooled, the methanol remov d by rotary evaporation, and the product dried as the trisodium salt by lyophylization.

EXAMPLE XXI

Preparation of mono-L-serinyl mesochlorin e_6

A. Mesochlorin e_6

Mesochlorin e_6 trimethyl ester was prepared according to the procedure of Fischer and Stern, Di Chemie Des Pyrroles, Volume II, second half, Leipzig 1940, Akademische Verlagsgesellschaft p. 102.

The mesochlorin e_6 trimethyl ester was then hydrolyzed to the free acid state by dissolution in refluxing n-propanol (0.1 ml/mg) and adding 6 fold equivalent amounts of 1N KOH. The product was collected by filtration, after cooling, as the potassium salt and dried under vacuum.

B. Mono-L-Serinyl Mesochlorin e_6

100 mg of the mesochlorin e_6 (free acid form) and 35 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were dissolved in 2 ml of N, N'-dimethyl formamide. After 5 minut s, 125 mg of L-serine b nzyl ester hydrochloride wer added, stirred vigorously until solution was complete, then allow d to stand at room temperature for 2 hours. At this time 0.5 ml of glacial acetic acid w re added, then 30 ml of methanol and 12 ml of H_2O.

The solution was applied to a C-18 reverse phase column (14 x 2 cm). The column was washed with H_2O (100 ml) then 4 ml of 1M NH_4OH, then with H_2O again (50 ml). Eluted product with MeOH/H_2O. Fractions eluted from th column with 30% to 80% MeOH contained product as well as carbodiimide activated chlorin as d termined by TLC on C-18 reverse phase plates with solv nt 70% MeOH/30% buff r (.01M sodium phosphate pH 6.85) V/V.

These fractions were pooled and enough 3 N NaOH was added to make the solution 0.1N in NaOH. After 1 hour, the hydrolysis was complete as determined by TLC in the above system. Removed the methanol by rotary evaporation and adjusted the pH of the solution to 7.5 with HCl. The chlorin solution was then reapplied to the same reverse phase column, washed with water, and eluted with MeOH/water using a stepwise gradient from 10 to 50% methanol. The fractions containing pure mono-L-serinyl chlorin was determined by TLC (R_f slightly greater than the unsubstituted chlorin) were pooled, the methanol removed by rotary evaporation, and the product dried as the trisodium salt by lyophylization.

Utilizing the aforementioned carbodiimide or the mixed anhydride methods of Exampies 8-21 the following preferred monoamide compounds of this invention are synthesized:

Chlorin Derivatives

(DL)-Serinyl-trans-mesochlorin IX
Glycyl-trans-mesochlorin IX
α-(DL)-Alanyl-trans-mesochlorin IX
β-Alanyl-trans-mesochlorin IX
ε-Amino-n-caproyl-mesochlorin IX
(D,L)-Serinyl chlorin e_6
(D,L)-Serinyl mesochlorin e_6
Glycyl chlorin e_6
Glycyl mesochlorin e_6
α-[D,L)-Alanyl chlorin e_6
α-(D,L) Alanyl mesochlorin e_6
β-Alanyl chlorin e_6
β-Alanyl mesochlorin e_6
ε-Amino-n-caproyl chlorin e_6
ε-Amino-n-caproyl mesochlorin e_6
(D,L)-Serinyl chlorin e_4
(D,L)-Serinyl mesochlorin e_4
(D,L)-Serinyl isochlorin e_4
(D,L)-Serinyl mesoisochlorin e_4
Glycyl chlorin e_4
Glycyl mesochlorin e_4
Glycyl isochlorin e_4
Glycyl mesoisochlorin e_4
α-(DL)-Alanyl chlorin e_4
α-(DL)-Alanyl mesochlorin e_4
α-(DL)-Alanyl isochlorin e_4
α-(DL)-Alanyl mesoisochlorin e_4
β-Alanyl chlorin e_4
β-Alanyl mesochlorin e_4
β-Alanyl isochlorin e_4
β-Alanyl mesoisochlorin e_4
ε-Amino-n-caproyl chlorin e_4
ε-Amino-n-caproyl mesochlorin e_4
ε-Amino-n-caproyl isochlorin e_4
ε-Amino-n-caproyl mesoisochlorin e_4
(D,L)-Serinylphotoprotoporphyrin IX
Glycylphotoprotoporphyrin IX
α-(D,L)-Alanylphotoprotoporphyrin IX
β-Alanylphotoprotoporphyrin IX
ε-Amino-n-caproylphotoprotoporphyrin IX
Threoninyl chlorin e_6

Tyrosyl chlorin e_6
Valyl chlorin e_6
Leucyl chlorin e_6
Isoleucyl chlorin e_6
Prolyl chlorin e_6
Methionyl chlorin e_6
Histidyl chlorin e_6
Arginyl chlorin e_6
Lysyl chlorin e_6
Glutaminyl chlorin e_6
4-hydroxyprolyl chlorin e_6
5-hydroxylysyl chlorin e_6
ϵ amino-n-caproyl chlorin e_6
γ aminobutanoyl chlorin e_6
3- methyl histidyl chlorin e_6
Alanyl 2-acetyl-chlorin e_6
Valyl 2-acetyl-chlorin e_6
Leucyl 2-acetyl-chlorin e_6
Isoleucyl 2-acetyl-chlorin e_6
Prolyl 2-acetyl-chlorin e_6
Methionyl 2-acetyl-chlorin e_6
Glycyl 2-acetyl-chlorin e_6
Serinyl 2-acetyl-chlorin e_6
Threoninyl 2-acetyl-chlorin e_6
Cysteinyl 2-acetyl-chlorin e_6
Tyrosyl 2-acetyl-chlorin e_6
Asparginyl 2-acetyl-chlorin e_6
Lysyl 2-acetyl-chlorin e_6
Arginyl 2-acetyl-chlorin e_6
Histidyl 2-acetyl-chlorin e_6
Glutaminyl 2-acetyl-chlorin e_6
4-hydroxy-prolyl 2-acetyl-chlorin e_6
5-hydroxy lysyl 2-acetyl-chlorin e_6
ϵ-amino-n-caproyl 2-acetyl-chlorin e_6
γ-aminobutanoyl 2-acetyl-chlorin e_6
3-methyl histidyl 2-acetyl-chlorin e_6
β-alanyl 2-acetyl-chlorin e_6
Alanyl 2 formyl chlorin e_6
Valyl 2 formyl chlorin e_6
Leucyl 2 formyl chlorin e_6
Isoleucyl 2 formyl chlorin e_6
Prolyl 2 formyl chlorin e_6
Methionyl 2 formyl chlorin e_6
Glycyl 2 formyl chlorin e_6
Serinyl 2 formyl chlorin e_6
Threoninyl 2 formyl chlorin e_6
Cysteinyl 2 formyl chlorin e_6
Tyrosyl 2 formyl chlorin e_6
Asparginyl 2 formyl chlorin e_6
Lysyl 2 formyl chlorin e_6
Arginyl 2 formyl chlorin e_6
Histidyl 2 formyl chlorin e_6
Glutaminyl 2 formyl chlorin e_6
4-hydroxy-prolyl 2 formyl chlorin e_6
5-hydroxy lysyl 2 formyl chlorin e_6
ϵ-amino-n-caproyl 2 formyl chlorin e_6
γ-aminobutanoyl 2 formyl chlorin e_6
3-methyl histidyl 2 formyl chlorin e_6

β-alanyl 2 formyl chlorin e_6
Alanyl Deuterochlorin e_6
Valyl Deuterochlorin e_6
Leucyl D uterochlorin e_6
Isoleucyl Deuterochlorin e_6
Prolyl Deuterochlorin e_6
Methionyl Deuterochlorin e_6
Glycyl Deuterochlorin e_6
Serinyl Deuterochlorin e_6
Threoninyl Deuterochlorin e_6
Cysteinyl Deuterochlorin e_6
Tyrosyl Deuterochlorin e_6
Asparginyl Deuterochlorin e_6
Lysyl Deuterochlorin e_6
Arginyl Deuterochlorin e_6
Histidyl Deuterochlorin e_6
Glutaminyl Deuterochlorin e_6
4-hydroxy-prolyl Deuterochlorin e_6
5-hydroxy lysyl Deuterochlorin e_6
ε-amino-n-caproyl Deuterochlorin e_6
γ-aminobutanoyl Deuterochlorin e_6
3-methyl histidyl Deuterochlorin e_6
β-alanyl Deuterochlorin e_6
valyl mesochlorin e_6
Leucyl mesochlorin e_6
Isoleucyl mesochlorin e_6
Prolyl mesochlorin e_6
Methionyl mesochlorin e_6
Serinyl mesochlorin e_6
Threoninyl mesochlorin e_6
Cysteinyl mesochlorin e_6
Tyrosyl mesochlorin e_6
Asparginyl mesochlorin e_6
Lysyl mesochlorin e_6
Arginyl mesochlorin e_6
Histidyl mesochlorin e_6
Glutaminyl mesochlorin e_6
4-hydroxy-prolyl mesochlorin e_6
5-hydroxy lysyl mesochlorin e_6
γ-aminobutanoyl mesochlorin e_6
3-methyl histidyl mesochlorin e_6

Porphyrin Derivatives

(D,L)-Serinylmesoporphyrin IX
Glycylmesoporphyrin IX
α-(DL)-Alanylmesoporphyrin IX
β-Alanylmesoporphyrin IX
ε-Amino-n-caproylmesoporphyrin IX
(D,L)-Serinylprotoporphyrin IX
Glycylprotoporphyrin IX
α-(D,L)-Alanylprotoporphyrin IX
β-Alanylprotoporphyrin IX
ε-Amino-n-caproylprotoporphyrin IX
(D,L)-Serinyldeuteroporphyrin IX
Glycyldeuteroporphyrin IX
α-(D,L)-Alanyldeuteroporphyrin IX
β-Alanyldeuteroporphyrin IX

ε-Amino-n-caproyldeuteroporphyrin IX
tetra- (D,L)-Serinylcoproporphyrin III
tetra- Glycylcoproporphyrin III
tetra- α-(D,L)-Alanylcoproporphyrin III
tetra- β-Alanylcoproporphyrin III
tetra- ε-Amino-n-caproylcoproporphyrin III
(D,L)-Serinylhematoporphyrin IX
Glycylhematoporphyrin IX
α-(D,L)-Alanylhematoporphyrin IX
β-Alanylhematoporphyrin IX
ε-Amino-n-caproylhematoporphyrin IX

Bacteriochlorin Derivatives

(D,L)-Serinylbacteriochlorin e_4
Glycylbacteriochlorin e_4
α-(DL)-Alanylbacteriochlorin e_4
β-Alanylbacteriochlorin e_4
ε-Amino-n-caproylbacteriochlorin e_4
(D,L)-Serinylbacterioisochlorin e_4
Glycylbacterioisochlorin e_4
α-(DL)-Alanylbacterioisochlorin e_4
β-Alanylbacterioisochlorin e_4
ε-Amino-n-caproylbacterioisochlorin e_4
(D,L)-Serinylbacteriochlorin e_6
Glycylbacteriochlorin e_6
α-(DL)-Alanylbacteriochlorin e_6
β-Alanylbacteriochlorin e_6
ε-Amino-n-caproylbacteriochlorin e_6

Other amino acid derivatives of the tetrapyrroles can also be prepared. The following amino acids can also be used to prepare the mono- di-, tri-, or where appropriate, the tetra-amino acid derivatives of the chlorins, porphyrins, or bacteriochlorins, employing the procedures of one of the aforementioned methods: piperidine-2-carboxylic acid, piperidine-6-carboxylic acid, pyrrole-2-carboxylic acid, pyrrole-5-carboxylic acid, piperidine-6-propionic acid, and pyrrole-5-acetic acid

Mixed amino acid derivatives of the tetrapyrroles can also be prepared. The various chlorin derivatives, porphyrin derivatives and bacteriochlorin derivatives can include any two or three of the following amino acids: glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, α-alanine, β-alanine, valine, leucine, isoleucine, proline, α-phenylalanine, β-phenylalanine, tryptophan, methionine, ε-amino-n-caproic acid, piperidine-2-carboxylic acid, pyrrole-5-carboxylic acid, piperidine-6-propionic acid, pyrrole-5-acetic acid.

Physical characteristics of the compounds (relative polarity) is measured by a standard chromatographic system. The chromatographic data (Rf values) were measured on Baker silica gel-C18 thin layer chromatographic plates, the particle size of which is 20 μM, and the coating thickness of which is 200 μM. The solvent system for these chromatographic runs consisted of 75% methanol, and 25% 0.01 M potassium phosphate buffer, pH 6.85. The compounds were spotted and dried on the plate as the sodium salts, at approximately neutral pH and minimum salt concentrations. The Rf values for the various derivatives are tabulated in TABLE 1. Spectroscopic data are indicated in TABLE 2.

TABLE 1

Rf VALUES		
Compounds	Derivative	Rf
Mesoporphyrin IX	--	.32
Mesoporphyrin IX	mono-α-alanyl	.44
Mesoporphyrin IX	mono-β-alanyl	.44
Mesoporphyrin IX	di-α-alanyl	.51
Mesoporphyrin IX	di-β-alanyl	.49
Mesoporphyrin IX	mono-glycycl	.47
Mesoporphyrin IX	di-seryl	.58
Mesoporphyrin IX	di-glycyl	.54
Mesoporphyrin IX	di-ε-aminocaproyl	.34
Hematoporphyrin IX	--	.78
Hematoporphyrin IX	mono-β-alanyl	.83
Hematoporphyrin IX	di-β-alanyl	.83
Chlorin e_6	--	.66
Chlorin e_6	di-L-α-serinyl	.78
2-formyl chlorin e_6	-----	0.74
2-acetyl chlorin e_6	-----	0.71
Deutero chlorin e_6	-----	0.79
Mesochlorin e_6	-----	0.69
2-formyl chlorin e_6	Mono-L-serinyl	0.87
2-acetyl chlorin e_6	Mono-L-serinyl	0.86
Deuterochlorin e_6	Mono-L-serinyl	0.90
Mesochlorin e_6	Mono-L-serinyl	0.73
Chlorin e_6	Mono-L-asparaginyl	0.72
Chlorin e_6	Mono-L-cysteinyl	0.93
Chlorin e_6	Mono-L-serinyl	0.72

TABLE II

Spectroscopic Absorption Data

Solvent in all cases is p-dioxane.

Compounds	Absorption Maxima (nm) in Visible Region	mM Extinction Coefficient (EmM) ± 10%	Soret Band nM
Photoprotoporphyrin IX isomer mixture	668	38	415
Pheophorbide a	667	35	408.6
Pyropheophorbide a	668	38	411.2
Trans-mesochlorin IX	643	60	388
Chlorin e_6	665.6	42	402
Hematoporphyrin derivative (HPD)	626	2.9	399
Mesochlorin e_6	651		399
2-acetyl-chlorin e_6	712,683		410
2-formyl-chlorin e_6	627		412
Deuterochlorin e_6	653		398
Chlorin e_6	666		402

Absorption data for the amino acid conjugates is identical to the parent chlorins.

The following protocol describes the procedure for the utilization of these new compounds of the present invention in the treatment of rat tumors.

EXAMPLE XXII

The photodynamic therapy experiments have been carried out on Buffalo rats, using the transplantabl tumor, Morris Hepatoma 7777. The tumors were transplanted subcutaneously on the outside of the thigh. During treatment, the tumors ranges in size between 1 and 2.5 cm in diameter.

The general treatment regime is as follows. The rats are injected with a solution of the chlorin prepar d as follows: 20 mg of the sodium salt of the chlorin was dissolved in 1 ml of 0.9% NaCl. The chlorin solution was then injected intravenously through the external jugular while the rat was anesthetized with ether. The volume of solution injected was calculated based upon the weight of the animal and the dosage, on a weight to weight basis, for the particular experiment. A specified time interval was then allowed to elapse befor light treatment was instigated.

Light treatment of the rats was without anesthesia. The rats were restrained, the hair removed in the treatment area and treated with laser light from a Cooper Aurora argon pumped, tunable dye laser.

The laser was equipped with a fiber optic light delivery system coupled to a microlens system developed by Dr. Daniel Doiron, D.R.D. Consulting, Santa Barbara, California.

The lens disperses the laser beam, providing a circular distribution of light with homogenous light intensity throughout the area of the incident light b am. The wavelength of light was adjusted using a Hartridge reversion sp ctroscope. The light intensity was determined using a Yellow Springs Instrument, Model 65A, radiometer.

The micro lens was positioned at such a distance from the skin of the animal so as to provide an illumination diameter of 1.5cm, and the light flux was varied by control of the laser output.

Subsequent to illumination, the animal was returned to its cage and, 24 hours later, it was treated

intravenously in the external jugular vein with 14 mg of Evans Blue dye, dissolved in 250 µl of 0.9% NaCl. Two hours aft r injection, the rat was sacrificed and the tumor cross-sectioned. The extent of tumor necrosis was assessed by the lack of dy uptake [1], and the depth of the necrotic cross section of the tumor was recorded in millimeters.

Table III summarizes the effects of these drugs on tumors and includes a range of wavelengths, dosages, intensities, and time intervals for treatment. This has been necessary, in order to attempt to establish the optimal conditions for phototherapy utilizing this new drug. The conditions described result in measurable and significant damage to the tumors.

In all cases except where noted, tissue damage occurred selectively to the tumor tissue as assayed by the Evans Blue method, even though, in nearly all cases, normal skin overlayed the tumor and the treatment area overlapped significant areas of normal muscle tissue.

The photodynamic therapy date is presented in tabular form. Column No. 2 is the total light dose administered in terms of Joules per square centimeter. Column No. 3 is the dose of chlorin administered in terms of mg of drug per kilogram of rat body weight. Column No. 4 is the time lapse between administration of drug and treatment with laser light. Column No. 5 is the wavelength of treatment light in nanometers. Column No. 6 is the intensity of the treatment light in milliwatts per square centimeter. In Column No. 7, $\bar{x}$ is the mean depth of necrosis in millimeters of the tumor tissue, i.e., the distance from the necrotic top of th tumor next to the skin to the necrotic edge of the tumor most distant from the skin.

S.D. is the standard deviation of $\bar{x}$.

(N) is the number of tumors or legs involved in the experiment.

Column No. 8 is the range of depth of necrosis in millimeters within the group.

(1) M.C. Berenbaum, Br. J. Cancer 45 : 571(1982)

TABLE III

Tumor	Joules/cm^2	Drug dose mg/kg	Time in hrs btwn drugs & light	Wave lnth nm	Intensity mW/cm^2	$\bar{x}$ s.d.	(n)	Range mm
			Mono Glycyl chlorin e_6					
7777	20	20	24	665	100	3.9±3.0	(5)	2-9 *
			Mono-L-α-alanyl chlorin e_6					
7777	20	20	24	665	100	3.8±1.8	(2)	2.5-5
			Mono-L-α-serinyl chlorin e_6					
7777	20	20	24	665	100	6.3±2.7	(6)	3-10
			Diglycyl chlorin e_6					
7777	20	20	24	665	100	4.7±1.0	(3)	3.5-5.5

* 3 of 8 tumors showed no necrosis due to drug and light.

EXAMPLE XXIII

The tr atment and evaluation proc dure is as follows:

DBA/2 Ha Ros-d + Ha mic with SmT-F transplanted tumors either in the exterior part of the hind leg or

the side of the mouse w re injected intravenously via the external jugular or the intraperitoneally with the photosensitizing drug. At the specified time after injection, the area over the tumor was shaved and the light treatment begun.

Light from a Copp r Aurora argon pumped tunable dye laser was administered via a micro lens system (developed by Dr. Daniel Doiron, D.R.D. Consulting, Santa Barbara, California) coupled through a quartz fiber to the laser, the optical properties of the lens are such that the light exits the lens in a circular pattern with homogenous intensity throughout the lighted area. The diameter of the lighted area is a function of the distance from the lens.

The light intensity was measured with a Yellow Springs Instrument Model 65 A Radiometer at the point of treatment. A 1.5 cm diameter circle of the animal's skin, centered as closely as possible over the tumor, was irradiated in all the experiments. The intensity, wavelength, and dosage of light is included in the data for individual groups of animals. Wavelengths are adjusted, using a Hartridge reversion spectroscope to within 1 nm of the stated value.

Twenty four hours after light treatment, each mouse received 5 mg of Evans Blue Dye intravenously [1]. After an additional two hours, the mice were sacrificed and the tumors were sectioned vertically through the center of the light treated area. Unaffected tumor was stained blue as was unaffected normal tissue. Necrotic or affected areas were white or red in appearance. Measurements on both the whole tumors and affected areas of the tumors were made vertically and horizontally with calipers to the nearest one half millimeter. The results of representative compounds are depicted in the following tables:

(1) M.C. Berenbaum. Br. J. Cancer. 45:571 (1982).

TABLE IV - MOUSE DATA

	COMPOUND USED	Mono-L-serinyl mes chlorin e6				
1	ANIMAL GROUP NO.	78	78	78	78	78
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5
4	SEX OF MOUSE	m	m	m	m	m
5	WT. OF MOUSE (gms)	23.3	25.8	21.0	22.8	26.4
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0	200.0	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0	300.0	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	651	651	651	651	651
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.00	0.90	0.75	0.55	1.05
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	0.60	0.55	0.65	0.45	0.45
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.45	0.30	0.30	0.20	0.25
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.30	1.30	0.30	0.90	1.30
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	1.20	1.00	0.80	0.70	0.85
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.65	0.70	0.65	0.60	0.60
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.80	0.10	0.60	0.00
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.40	0.10	0.60	0.00
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.30	0.10	0.20	0.00
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	no effect	red skin effect 0.9 x 0.9cm			red skin effect 0.6x0.6cm no effect on the tumor

TABLE V - MOUSE DATA

	COMPOUND USED	Mono-L-serinyl 2-acetyl chlorin e6	
1	ANIMAL GROUP NO.	81	81
2	DATE EXPERIMENT STARTED	--	--
3	MOUSE NO.	1	2
4	SEX OF MOUSE	m	m
5	WT. OF MOUSE (gms)	26.5	21.0
6	DRUG DOSE (mg/kg)	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	680	680
14	DATE ANIMAL INJECTED WITH DRUG	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	0.80	0.80
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	0.45	0.60
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.40	0.40
18	DATE ANIMAL SACRIFICED	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.20	0.90
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	0.90	0.70
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.60	0.40
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.00
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.00
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.00
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	no effect	no effect

TABLE VI - MOUSE DATA

	COMPOUND USED	Mono-L-serinyl deuterochlorin e6				
1	ANIMAL GROUP NO.	82	82	82	82	82
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5
4	SEX OF MOUSE	m	m	m	m	m
5	WT. OF MOUSE (gms)	25.7	23.2	21.3	20.5	24.4
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0	200.0	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0	300.0	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	655	655	655	655	655
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.40	1.75	1.90	1.45	1.35
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	1.15	1.10	0.65	1.05	0.85
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.75	1.00	0.20	0.90	0.65
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.70	1.80	2.20	1.75	1.50
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	0.80	1.15	1.00	1.25	0.85
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.60	0.60	0.80	0.50	0.65
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.30	0.40	0.40	1.00	0.00
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.35	0.40	0.40	1.15	0.00
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.15	0.20	0.20	0.20	0.00
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT					no effect

TABLE VII - MOUSE DATA

	COMPOUND USED	Mono-L-asparaginyl chlorin e6				
1	ANIMAL GROUP NO.	83	83	83	83	83
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5
4	SEX OF MOUSE	m	m	m	m	m
5	WT. OF MOUSE (gms)	25.4	25.0	25,8	24.6	24.1
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0	200.0	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0	300.0	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	665
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.30	1.20	1.30	1.25	1.00
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	0.90	0.90	1.05	0.75	0.70
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.60	0.55	0.60	0.60	0.50
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.05	1.40	1.60	1.60	1.30
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	0.90	0.85	0.80	0.75	0.90
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.65	0.65	0.60	0.65	0.60
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	1.05	1.40	1.10	1.60	1.05
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.90	0.85	0.50	0.75	0.60
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.50	0.60	0.35	0.65	0.45
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	skin effect 0.65 x 0.60cm	skin effect 0.8 x 0.9cm		skin effect 0.95 x 0.95cm; muscle damage	skin effect 0.5 x 0.5cm

TABLE VIII - MOUSE DATA

	COMPOUND USED	Mono-L-seriny1-2-formyl chlorin e6			
1	ANIMAL GROUP NO.	85	85	85	85
2	DATE EXPERIMENT STARTED	--	--	--	--
3	MOUSE NO.	1	2	3	4
4	SEX OF MOUSE	m	m	m	m
5	WT. OF MOUSE (gms)	26.0	20.5	20.2	28.8
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	690	690	690	690
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.60	1.70	1.80	1.60
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	1.00	1.10	1.20	1.00
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.70	0.75	0.60	0.70
18	DATE ANIMAL SACRIFICED	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.60	1.60	1.00	1.70
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	1.05	1.10	1.30	1.10
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.75	0.80	0.80	0.80
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.40	1.30	0.90	0.00
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.30	0.60	0.80	0.00
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.15	0.25	0.30	0.00
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT				no effect

TABLE IX - MOUSE DATA

	COMPOUND USED	Mono-L-cysteinyl chlorin e6				
1	ANIMAL GROUP NO.	86	86	86	86	86
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5
4	SEX OF MOUSE	m	m	m	m	m
5	WT. OF MOUSE (gms)	26.0	26.2	27.1	22.2	26.0
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	200.0	200.0	200.0	200.0	200.0
12	LIGHT DOSE (J/cm^2)	300.0	300.0	300.0	300.0	300.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	665
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.45	1.60	2.05	0.90	1.80
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	1.00	1.20	1.60	0.85	1.30
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.75	0.65	0.90	0.60	0.70
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.40	1.80	1.80	1.00	2.00
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	1.00	1.05	1.40	1.10	1.30
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.80	0.70	0.80	0.75	0.80
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	1.40	1.60	1.60	1.00	1.85
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	1.00	1.05	1.10	1.10	1.20
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.80	0.45	0.60	0.70	0.75
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	red skin 1.3 x 1.0cm; some muscle damage	skin effect 1.6 x 1.2cm; some muscle damage	skin effect 1.4 x 1.4cm	skin effect 0.9 x 0.9cm some muscle damage	skin effect 1.5 x 1.4 cm

The results of Table IV - IX are summarized in Table X.

TABLE X

compound	drug dose mg/kg	method of injection	time in hrs between drug dose & light	tumor type	light intensity mW/cm²	light dose J/cm²	wave-length nm	(n)	$\bar{x}$ ± s.d. (cm)	range cm
mono-l-aspartyl chlorin e6	100	iv	24	SMT-F	200	300	665	(5)	0.51±0.12	0.35-0.65
mono-l-cysteinyl chlorin e6	100	iv	24	SMT-F	200	300	665	(5)	0.66±0.14	0.45-0.80
mono-l-serinyl-2-acetyl chlorin e6	100	iv	24	SMT-F	200	300	680	(2)	0.00	0.00
mono-l-serinyl-2-formyl chlorin e6	100	iv	24	SMT-F	200	300	690	(4)	0.18±0.13	0.00-0.30
mono-l-serinyl deuterochlorin e6	100	iv	24	SMT-F	200	300	655	(5)	0.15±0.09	0.00-0.20
mono-l-serinyl mesochlorin e6	100	iv	24	SMT-F	200	300	651	(5)	0.12±0.13	0.00-0.30

TABLE XI - MOUSE DATA

	COMPOUND USED	Mono-L- -seriryl chlorin e6					
1	ANIMAL GROUP NO.	49	49	49	49	49	49
2	DATE EXPERIMENT STARTED	--	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5	6
4	SEX OF MOUSE	m	f	f	f	f	f
5	WT. OF MOUSE (gms)	24.8	22.1	20.2	16.4	20.7	22.7
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	75.0	75.0	75.0	75.0	75.0	75.0
12	LIGHT DOSE (J/cm^2)	20.0	20.0	20.0	20.0	20.0	20.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	665	665
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	0.00	1.40	2.00	1.50	1.60	1.60
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	0.00	0.80	1.00	0.90	1.05	0.90
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.00	0.65	0.60	0.60	0.65	0.70
18	DATE ANIMAL SACRIFICED	--	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	0.00	1.60	2.20	1.90	1.20	1.70
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	0.00	0.85	1.15	1.15	1.05	1.05
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.00	0.45	0.65	0.60	0.80	0.80
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	1.60	1.20	1.50	1.20	1.50
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.85	1.00	1.20	1.05	0.95
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.45	0.50	0.50	0.50	0.50
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	Died of the ether	leg swollen, skin pink over the treatment area, top 2/3 of tumor red.	leg swollen, skin pink over treatment area, tumor red on top.	leg swollen, skin pink over the treatment site, tumor red on top	leg swollen, skin pink over treatment site, top 2/3 of tumor red	leg swollen, skin pink over treated site, top 2/3 of tumor red.

TABLE XI - MOUSE DATA (cont.)

	COMPOUND USED	Mono-L- -serinyl chlorin e6				
1	ANIMAL GROUP NO.	49	49	49	49	49
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	7	8	9	10	11
4	SEX OF MOUSE	f	f	f	f	m
5	WT. OF MOUSE (gms)	20.9	19.4	20.6	20.2	19.6
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	0.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	0.0
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	0.0
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	75.0	75.0	75.0	75.0	0.0
12	LIGHT DOSE (J/cm^2)	20.0	20.0	20.0	20.0	0.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	0.0
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.50	0.90	1.70	1.30	0.00
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	1.25	0.75	0.95	0.90	0.00
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.70	0.70	0.65	0.60	0.00
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.90	1.45	1.70	1.70	0.00
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	1.35	0.95	1.00	1.10	0.00
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.85	0.80	0.95	0.85	0.00
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	1.50	1.30	1.40	1.10	0.00
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	1.00	0.95	0.90	0.95	0.00
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.70	0.60	0.60	0.45	0.00
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	leg swollen, skin pink over treatment site, top ½ of tumor red	leg swollen, skin pink over treatment area, top ⅔ of tumor red	leg swollen, skin pink over treatment site, top ⅔ of tumor red	leg swollen, skin pink over treatment area, top ½ of tumor red	died of ether after the injection

TABLE XII - MOUSE DATA

	COMPOUND USED	Mono glycyl chlorin e6				
1	ANIMAL GROUP NO.	47	47	47	47	47
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	1	2	3	4	5
4	SEX OF MOUSE	f	f	f	f	f
5	WT. OF MOUSE (gms)	20.4	18.7	21.3	19.6	18.4
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	75.0	75.0	75.0	75.0	75.0
12	LIGHT DOSE (J/cm^2)	20.0	20.0	20.0	20.0	20.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	665
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.60	1.10	1.80	1.85	1.35
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	1.00	0.95	1.10	1.50	1.05
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.80	0.65	0.60	0.85	0.65
18	DATE ANIMAL SACRIFICED	--	--	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.20	0.00	1.65	1.40	1.25
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	0.90	0.00	1.40	1.00	0.95
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.90	0.00	1.00	0.90	0.65
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.70	0.00	0.40	0.30	0.70
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.60	0.00	0.60	0.60	0.80
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.30	0.00	0.20	0.20	0.25
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT		died from the dye injection; cannot read			

TABLE XII - MOUSE DATA (cont.)

	COMPOUND USED	Mono glycyl chlorin e6				
1	ANIMAL GROUP NO.	47	47	47	47	47
2	DATE EXPERIMENT STARTED	--	--	--	--	--
3	MOUSE NO.	6	7	8	9	10
4	SEX OF MOUSE	f	f	f	f	f
5	WT. OF MOUSE (gms)	19.6	19.1	20.1	19.8	19.6
6	DRUG DOSE (mg/kg)	100.0	100.0	100.0	100.0	100.0
7	METHOD OF DRUG INTRODUCTION	iv	iv	iv	iv	iv
8	TIME BETW. DRUG INTRODUCTION + LIGHT TREATMENT (hrs)	24.0	24.0	24.0	24.0	24.0
9	TUMOR TYPE	SMT-F	SMT-F	SMT-F	SMT-F	SMT-F
10	POSITION OF TUMOR ON ANIMAL	r leg	r leg	r leg	r leg	r leg
11	LIGHT TREATMENT INTENSITY (mW/cm^2)	75.0	75.0	75.0	75.0	75.0
12	LIGHT DOSE (J/cm^2)	20.0	20.0	20.0	20.0	20.0
13	WAVE LENGTH USED TO TREAT TUMOR (nm)	665	665	665	665	665
14	DATE ANIMAL INJECTED WITH DRUG	--	--	--	--	--
15	LENGTH OF TUMOR ON INJECTION DATE (cm)	1.30	1.35	1.35	1.35	1.30
16	WIDTH OF TUMOR ON INJECTION DATE (cm)	0.95	1.00	0.90	1.05	0.90
17	DEPTH OF TUMOR ON INJECTION DATE (cm)	0.70	0.80	0.60	0.60	0.50
18	DATE ANIMAL SACRIFICED	--	---	--	--	--
19	LENGTH OF TUMOR ON SACRIFICE DATE (cm)	1.05	1.35	1.40	1.35	1.20
20	WIDTH OF TUMOR ON SACRIFICE DATE (cm)	1.00	1.00	1.10	1.00	1.10
21	DEPTH OF TUMOR ON SACRIFICE DATE (cm)	0.65	0.90	0.80	0.80	0.70
22	LENGTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.75	0.00	0.00	0.35
23	WIDTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.80	0.00	0.00	0.90
24	DEPTH OF EFFECT UPON TUMOR ON SACRIFICE DATE (cm)	0.00	0.90	0.00	0.00	0.25
25	COMMENTS AS RESULT OF TUMOR ASSESSMENT	no effect	not clear if the effect is due to the treatment.	no effect	no effect	

The results Of Table XI - XII are summarized in Table XIII.

TABLE XIII

Compound	Drug Dose mg/kg	Tumor Type	Time in Hrs. between Drug Introduction & Light Treatment	Position of Tumor in animal	Light Intensity in mW/cm^2	Light Dose in J/cm^2	Wavelength used to treat tumors in nm	Depth in cm of effect upon tumor	S.D.	n	range
L-α mono-seriny1 chlorin e6	100	Smt-f	24	rt. leg	75.0	20.0	665	0.53	± 0.09	9	0.45-0.70
L-α monoglycl chlorin e6	100	Smt-f	24	rt. leg	75.0	20.0	665	0.15	± 0.11	8	0.0-0.3

The preparation of pharmacological dosages for the administration of the active ingredient, that is th amino acid porphyrin adducts, which were prepared in Examples 1-21 hereinabove, is as follows:

EXAMPLE XXIV

A tablet base was prepared by blending the following ingredient in the proportion by weight indicated:

	Grams
Sucrose, USP	80.3
Tapioca Starch	13.2
Magnesium Stearate	4.4

Into this base, there was blended sufficient amino acid porphyrin adducts to provide tablets each containing 100 mg. of active ingredient.

EXAMPLE XXV

A blend was prepared containing the following ingredients:

Calcium phosphate	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate, USP	5.2
Lactose, U.S.P.	5.2
Potato Starch	5.2
Magnesium Stearate A	0.8
Magnesium Stearate B	0.32
Porphyrin Amino Acid Adducts	20

This blend was divided and formed into capsules each containing 25 mg of active ingredient.

EXAMPLE XXVI

To a commercially available raspberry flavored sugar syrup is added the equivalent of 40 mg of th amino acid porphyrin adduct per milliliter and the mixture is homogenized in a mechanical device for this purpose. This mixture is especially suitable for oral administration containing 200 mg of the active ingredient.

EXAMPLE XXVII

A sterile solution of the following composition is prepared: 200 mg of the sodium salt of the amino acid porphyrin adduct is dissolved in a 0.9% NaCl solution so that the final concentration is 20 mg/ml.

This solution is suitable for I.V. and I.M. administration.

EXAMPLE XXVIII

The sodium salt of the amino acid porphyrin adduct is dissolved in 0.9% NaCl solution so that the final concentration is 5 mg/ml. This is placed in an aerosal dispenser with a hydrocarbon propellant. This preparation is suitable for topical application.

EXAMPLE XXIX

PREPARATION OF A METAL SALT

The sodium salt of the porphyrin amino acid adduct is prepared by dissolving said adduct in water containing an equimolar amount of sodium hydroxide and freeze drying the resulting mixture.

In this fashion, other metal salts are prepared including potassium, calcium, and lithium salts.

PREPARATION OF AN ACID SALT

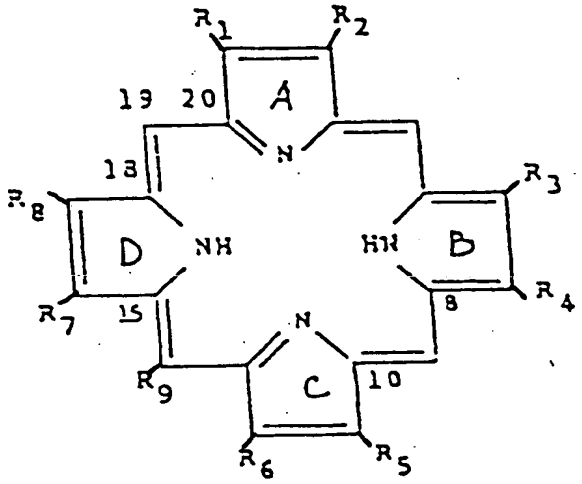
Th amino acid porphyrin adduct described in the preceding xamples are converted to acid salts, e.g., hydrochloride, by dissolving in an aqueous solution containing an equivalent amount of acid, e.g., hydrochloric acid, and the solution is evaporated to dryness to obtain th solid salt. Alternately, alcoholic solutions of hydrogen chloride gas, dissolv d in thanol can b used in lieu of the aqueous acid solution

and the acid salt is obtained by evaporation of the solvent or crystallization from the alcohol, e.g., by addition of a non-solvent.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

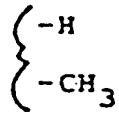
1. A therapeutic composition comprising a fluorescent mono, di or polyamide of an aminomonocarboxylic acid and a tetrapyrrole compound of the formula:



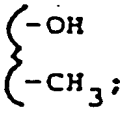
or salt thereof

or the corresponding di- or tetrahydrotetrapyrroles and a pharmaceutically acceptable carrier therefor; wherein

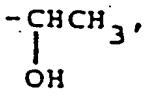
R_1 is methyl;



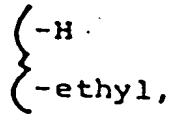
or

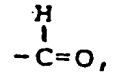


R_2 is H, vinyl, ethyl,



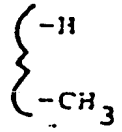
acetyl,



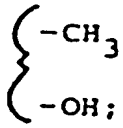


$CH_2CH_2CO_2H$, or =CHCHO;

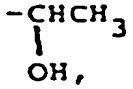
R_3 is methyl



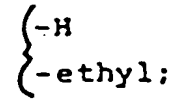
or



R_4 is H, vinyl, ethyl,



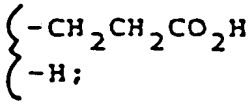
$CH_2CH_2CO_2H$, =CHCHO; or



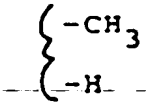
R_5 is methyl;

R_6 is H, $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ or CO_2H;

R_7 is $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$, or



R_8 is methyl or



R_9 is H, COOH, CH_2COOH or methyl;

provided that when R_1, R_2, R_3, R_4, R_7 and R_8 represent two substituents or are divalent and attached to the same carbon, the respective pyrrole ring to which they are attached is a dihydropyrrole;

R is lower alkyl or benzyl;

with the proviso that at least one of R_1-R_9 includes a free carboxyl group, and that amide bonds (1 to 4) are formed between the amino group of the aminomonocarboxylic acid and one of the carboxy groups of the tetrapyrrole; with the proviso that the tetrapyrrole residue is not pheophorbide a.

2. The composition according to claim 1 wherein the amino acid is an alpha amino acid.

3. Composition according to claim 1 or 2 wherein the tetrapyrrole is a porphyrin, chlorin or bacteriochlorin.

4. Composition according to any of claims 1 to 3, wherein the amide-containing substituents are asymmetrically arranged on the tetrapyrrole molecule.

5. Composition according to claim 1 wherein the amide is:

diserinyl mesophorphyrin IX,

diglycyl mesoporphyrin IX,

di-α-(DL)-alanyl mesoporphyrin IX,

di-β-alanyl mesoporphyrin IX,

di-ε-amino-n-caproyl mesoporphyrin IX,

diglycyl trans-mesochlorin IX,

diglycyl trans-mesochlorin e_6,

diglycyl mesochlorin e_4,

diglycyl hematoporphyrin IX,

diglycyl chlorin e_6,

diglycyl protoporphyrin IX,

diglycyl deuteroporphyrin,

di-α-(DL)-alanyl trans-mesochlorin IX,

di-α-(DL)-alanyl mesochlorin e_6,

di-α-(DL)-alanyl mesochlorin e_4,

di-α-(DL)-alanyl hematoporphyrin IX,

di-α-(DL)-alanyl chlorin e_6,

di-α-(DL)-alanyl protoporphyrin IX,

di-α-(DL)-alanyl deuteroporphyrin,

di-β-(DL)-alanyl trans-mesochlorin IX,

di-β-(DL)-alanyl mesochlorin e_6,

di-β-(DL)-alanyl mesochlorin e_4,

di-β-(DL)-alanyl hematoporphyrin IX,

di-β-(DL)-alanyl chlorin e_6,

di-β-(DL)-alanyl protoporphyrin IX,

di-β-(DL)-alanyl deuteroporphyrin,

di-L-α-serinyl chlorin e_6,

di-L-α-serinyl trans-mesochlorin e_6,

di-L-α-serinyl trans-mesochlorin IX,

di-L-α-serinyl trans-mesochlorin e_4,

di-L-α-serinyl hematoporphyrin IX,

di-L-α-serinyl protoporphyrin IX,

di-L-α-serinyl deuteroporphyrin,

di-ε-amino-n-caproyl-hematoporphyrin IX,

di-ε-amino-n-caproyl-chlorin e_6,

di-ε-amino-n-caproyl-protoporphyrin IX,

di-ε-amino-n-caproyl-deuteroporphyrin,

mono-L-serinyl mesochlorin e_6,

mono-L-serinyl Deuterochlorin e_6,

mono-L-serinyl-2-formyl chlorin e_6,

mono-L-serinyl-2-acetyl chlorin e_6,

mono-L-cysteinyl chlorin e_6,

mono-L-asparaginyl chlorin e_6 ,

mono serinyl chlorin e_6,

mono-(DL)glycyl chlorin e_6,

alanyl chlorin e_6,

mono-L-valyl chlorin e_6,

mono-L-leucyl chlorin e_6,

mono-L-isoleucyl chlorin e_6,

mono-L-prolyl chlorin e_6,

mono-L-methionyl chlorin e_6,

mono-L-threoninyl chlorin e_6,

tyrosyl chlorin e_6,

glutaminyl chlorin e_6,

lysyl chlorin e_6,

arginyl chlorin e_6,

histidyl chlorin e_6,

β-alanyl chlorin e_6,

mono-ϵ-amino-n-caproyl chlorin e_6,

monoglycyl mesoporphyrin IX,

mono alanyl mesoporphyrin IX,

mono-β-alanyl mesoporphyrin IX,

mono-ϵ-amino-n-caproyl mesoporphyrin IX,

mono-β-alanyl-hematoporphyrin IX,

threoninyl-2-formylchlorin e_6,

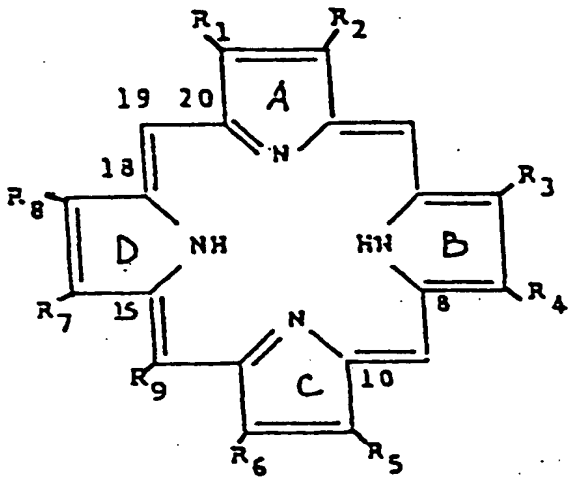
mono-L-threoninyl deuterochlorin e_6, or

mono-L-threoninyl mesochlorin e_6,

6. Use of a fluorescent mono, di or polyamide of an aminomonocarboxylic acid and a tetrapyrrole containing one or two carboxy groups of the structure as claimed in any of claims 1 to 5, or a salt thereof, and a pharmaceutically acceptable carrier therefor, for the preparation of a therapeutic composition for photodiagnosis and/or phototherapy of tumors.

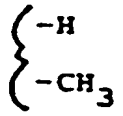
Claims for the following Contracting State : AT

1. Use of a fluorescent mono, di or polyamide of an aminomonocarboxylic acid and a tetrapyrrole compound of the formula:

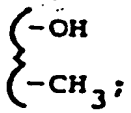


or salt thereof
or the corresponding di- or tetrahydrotetrapyrroles, and a pharmaceutically acceptable carrier therefor; wherein

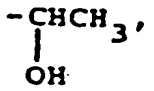
R_1 is methyl;



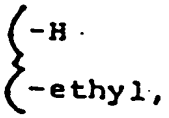
or

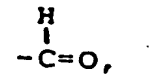


R_2 is H, vinyl, ethyl,

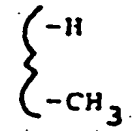


acetyl,

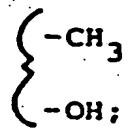




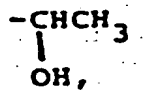
$CH_2CH_2CO_2H$, or $=CHCHO$;
R_3 is methyl



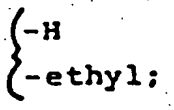
or



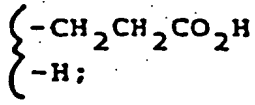
R_4 is H, vinyl, ethyl,



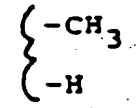
$CH_2CH_2CO_2H$, $=CHCHO$; or



R_5 is methyl;
R_6 is H, $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ or CO_2H;
R_7 is $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$, or



R_8 is methyl or

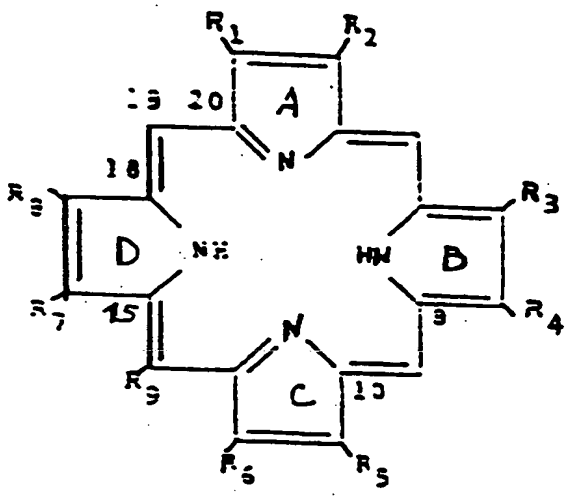


R_9 is H, COOH, CH_2COOH or methyl;
provided that when R_1, R_2, R_3, R_4, R_7 and R_8 represent two substituents or are divalent and attached to the same carbon, the respective pyrrole ring to which they are attached is a dihydropyrrole;
R is lower alkyl or benzyl;
with the proviso that at least one of R_1-R_9 includes a free carboxyl group, and that amide bonds (1 to 4) are formed between th amino group of the aminomonocarboxylic acid and one of the carboxy groups of the tetrapyrrole; with the proviso that the tetrapyrrole residue is not pheophorbide a; for the preparation of a therapeutic composition for photodiagnosis and/or phototherapy of tumors.

2. Use according to claim 1 , characterized in, that the amino acid is an alpha amino acid.

Patentansprüche
Patentansprüche für f lgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Therap utische Zusammensetzung, enthalt nd ein fluoreszierendes Mono-, Di- oder Polyamid einer Aminomonocarbonsäure und einer Tetrapyrrol-Verbindung der Formel



oder eines Salzes davon
oder der entsprechenden Di- oder Tetrahydrotetrapyrrole, und einen pharmazeutisch akzeptablen Träger dafür, wobei
R_1 Methyl,

$$\begin{cases} -H \\ -CH_3 \end{cases}$$

oder

$$\begin{cases} -OH \\ -CH_3 \end{cases}$$

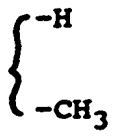
ist;
R_2 Wasserstoff, Vinyl, Ethyl,

$$-\underset{\underset{OH}{|}}{CHCH_3} ,$$

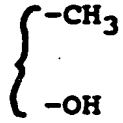
Acetyl,

$$\begin{cases} -H \\ \\ -Ethyl \end{cases} , \quad -\overset{H}{\underset{|}{C}}=O,$$

$CH_2CH_2CO_2H$ oder = CHCHO ist;
R_3 Methyl ,

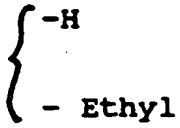


oder

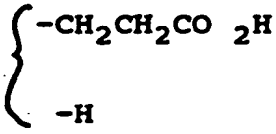


ist;
R_4 Wasserstoff, Vinyl, Ethyl,

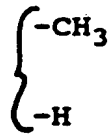
$CH_2CH_2CO_2H$, = CHCHO oder



ist;
R_5 Methyl ist;
R_6 Wasserstoff, CH_2CH_2COH, $CH_2CH_2CO_2R$ oder CO_2H ist;
R_7 $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ oder



ist;
R_8 Methyl oder



ist;

R_9 Wasserstoff, COOH, CH_2, CH_2COOH oder Methyl ist; unter der Voraussetzung, daß, wenn R_1, R_2, R_3, R_4, R_7 und R_8 zw i Substituenten darstellen oder divalent sind und am gleichen Kohlenstoff gebunden ist, der betreffende Pyrrolring, an den si gebunden sind, ein Dihydropyrrol ist;

R ein niedriger s Alkyl oder Benzyl ist;

unter der Voraussetzung, daß mind stens einer von R_1 - R_9 ein freie Carboxylgruppe enthält, und daß zwischen der Aminogruppe der Aminomonocarbonsäure und den Carboxygruppen des Tetrapyrrols Amidbindungen (1 bis 4) gebildet werden; unter der Voraussetzung daß der Tetrapyrrolrest nicht Pheophorbid a ist.

2. Zusammensetzung nach Anspruch 1, in der die Aminosäure eine alpha-Aminosäure ist.
Di--α-Serinyl-trans-mesochlorin IX
Di-L-α-Serinyl-trans-Mesochlorin e_4
Di-L-α-Serinyl-Hematoporphyrin IX
Di-L-α-Serinyl-Protoporphyrin IX
Di-L-α-Serinyl-Deuteroporphyrin
Di-ε-Amino-n-Caproyl-Hematoporphyrin IX
Di-ε-Amino-n-Caproyl-Chlorin e_6
Di-ε-Amino-n-Caproyl-Protoporphyrin IX
Di-ε-Amino-n-Caproyl-Deuteroporphyrin
Mono-L-Serinyl-Mesochlorin e_6
Mono-L-Serinyl-Deuterochlorin e_6
Mono-L-Serinyl-2-Formyl-Chlorin e_6
Mono-L-Serinyl-2-Acetyl-Chlorin e_6
Mono-L-Cysteinyl-Chlorin e_6
Mono-L-Asparaginyl-Chlorin e_6
Mono-Serinyl-Chlorin e_6
Mono-(DL)-Glycyl-Chlorin e_6
Alanyl-Chlorin e_6
Mono-L-Valyl-Chlorin e_6
Mono-L-Leucyl-Chlorin e_6
Mono-L-Isoleucyl-Chlorin e_6
Mono-L-Prolyl-Chlorin e_6
Mono-L-Methionyl-Chlorin e_6
Mono-L-Threoninyl-Chlorin e_6
Tyrosyl-Chlorin e_6
Glutaminyl-Chlorin e_6
Lysyl-Chlorin e_6
Arginyl-Chlorin e_6
Histidyl-Chlorin e_6
β-Alanyl-Chlorin e_6
Mono-ε-Amino-n-Caproyl-Chlorin e_6
Monoglycyl-Mesoporphyrin IX
Mono-Alanyl-Mesoporphyrin IX
Mono-β-Alanyl-Mesoporphyrin IX
Mono-ε-Amino-n-Caproyl-Mesoporphyrin IX
Mono-β-Alanyl-Hematorporphyrin IX
Threoninyl-2-Formylchlorin e_6

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, in der das Tetrapyrrol ein Porphyrin, Chlorin oder Bacteriochlorin ist.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, in der die Amid-haltigen Substituenten asymmetrisch am Tetrapyrrol-Molekül angeordnet sind.

5. Zusammensetzung nach Anspruch 1, in der das Amid

Diserinyl-Mesophorphyrin IX
Diglycyl-Mesoporphyrin IX

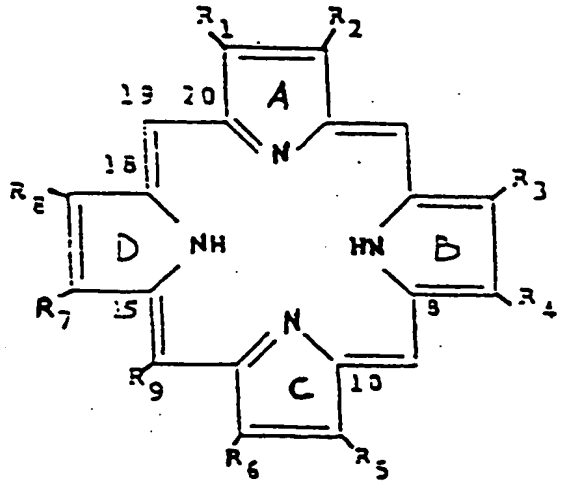
Di-α-(D,L)-Alanyl-Mesoporphyrin IX
Di-β-Alanyl-Mesoporphyrin IX
Di-ε-Amino-n-Caproyl-Mesoporphyrin IX
Diglycyl-trans-Mesochlorin IX
Diglycyl-trans-Mesochlorin e_6
Diglycyl-Mesoschlorin e_4
Diglycyl-Hemaporphyrin IX
Diglycyl-Chlorin e_6
Diglycyl-Protoporphyrin IX
Diglycyl-Deuteroporphyrin
Di-α-(DL)-Alanyl-trans-Mesochlorin IX
Di-α-(DL)-Alanyl-Mesochlorin e_6
Di-α-(DL)-Alanyl-Mesochlorin e_4
Di-α-(DL)-Alanyl-Hematoporphyrin IX
Di-α-(DL)-Alanylchlorin e_6
Di-α-(DL)-Alanyl-Protoporphyrin IX
Di-α-(DL)-Alanyl-Deuteroporphyrin
Di-β-(DL)-Alanyl-trans-Mesochlorin IX
Di-β-(DL)-Alanyl-Mesochlorin e_6
Di-β-DL)-Alanyl-Mesochlorin e_4
Di-β-(DL)-Alanyl-Hematoporphyrin IX
Di-β-(DL)-Alanyl-Chlorin e_6
Di-β-(DL)-Alanyl-Protoporphyrin IX
Di-L-α-Serinyl-trans-Mesochlorin e_6
Mono-L-Threoninyl-Deuterochlorin e_6 oder
Mono-L-Threoninyl-Mesochlorin e_6

ist.

6. Verwendung eines fluoreszierenden Mono-, Di- oder Polyamids einer Aminomonocarbonsäure und eines Tetrapyrrols, das eine oder zwei Carboxygruppen enthält, gemäß der in einem der Ansprüche 1 bis 5 beanspruchten Struktur, oder eines Salzes davon, und eines pharmazeutisch akzeptablen Trägers dafür, zur Herstellung einer therapeutischen Zusammensetzung für Photodiagnose und/oder für Phototherapie von Tumoren.

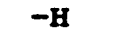
Patentansprüche für folgenden Vertragsstaat : AT

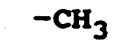
1. Verwendung eines fluoreszierenden Mono-, Di- oder Polyamids einer Aminomonocarbonsäure und einer Tetrapyrrol-Verbindung der Formel



oder ein s Salzes davon,
oder der entsprechenden Di- od r Tetrapyrrol und ines pharmazeutisch akzeptablen Trägers dafür, wobei

R_1 Methyl;





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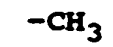
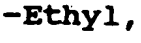
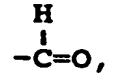


ist;

R_2 Wasserstoff, Vinyl, Ethyl,

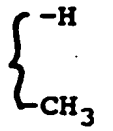
Acetyl,





$-CH_2CH_2CO_2H$ oder = CHCHO ist;

R_3 Methyl,



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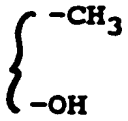
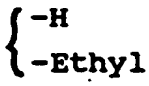


ist;

R_4 Wasserstoff, Vinyl, Ethyl,

$-CH_2CH_2CO_2H$, $=CHCHO$ oder

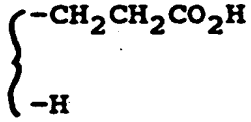


ist;

R_5 Methyl ist;

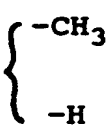
R_6 Wasserstoff, $-CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ oder CO_2H ist;

R_7 $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ oder



ist;

R_8 Methyl oder



ist;

R_9 Wasserstoff, COOH, CH_2COOH oder Methyl ist;

unter der Voraussetzung, daß, wenn R_1, R_2, R_3, R_4, R_7 und R_8 zwei Substituenten darstellen oder divalent und am gleichen Kohlenstoff gebunden sind, der betreffende Pyrrolring, an den sie gebunden sind, ein Dihydropyrrol ist;

R ist ein niedrigeres Alkyl oder Benzyl,

unter der Voraussetzung, daß mindestens einer von R_1 bis R_9 eine freie Carboxylgruppe enthält, und daß zwischen der Aminogruppe der Aminomonocarbonsäure und einer der Carboxygruppen d s Tetrapyrrols Amidverbindungen (1 bis 4) gebildet werden; unter der Voraussetzung, daß der Tetrapyrrolring nicht Pheophorbid a ist;

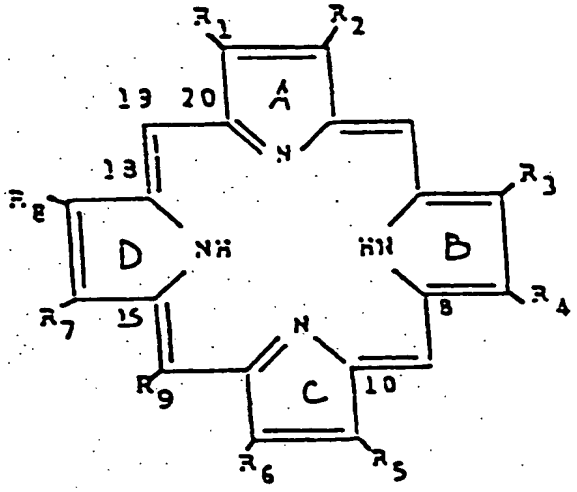
zur Herstellung einer therapeutischen Zusammensetzung für Fotodiagnose und/oder die Fototherapie von Tumoren.

2. Verwendung gemäß Anspruch 1,
dadurch gekennzeichnet,
daß die Aminosäure eine alpha-Aminosäure ist.

Revendications

R vendications pour les Etats c ntractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition thérapeutique comprenant un mono-, di- ou polyamide fluorescent d'un acide aminomonocarboxylique et d'un composé d tétrapyrrole représenté par la formul :



ou un sel de celui-ci,
ou les di- ou tétrahydrotétrapyrroles correspondants ; et
un support pharmaceutiquement acceptable pour celui-ci ;
où :

- R_1 représente méthyle,

$$\begin{cases} -H \\ -CH_3 \end{cases}$$

ou

$$\begin{cases} -OH \\ -CH_3 \end{cases} ;$$

- R_2 représente H, vinyle, éthyle,

$$-\underset{\underset{OH}{|}}{CHCH_3},$$

acétyle,

$$-\underset{\underset{O}{\|}}{\overset{\overset{H}{|}}{C}},$$

$CH_2CH_2CO_2H$, ou $=CHCHO$;

$$\begin{cases} -H \\ -\text{éthyle} \end{cases},$$

- R_3 représente méthyle,

$$\begin{cases} -H \\ -CH_3 \end{cases}$$

ou

$$\begin{cases} -CH_3 \\ -OH \end{cases};$$

- R_4 représente H, vinyle, éthyle,

$$-\underset{\underset{OH}{|}}{CHCH_3},$$

$CH_2CH_2CO_2H$, =CHCHO, ou

$$\begin{cases} -H \\ -\text{éthyle} \end{cases};$$

- R_5 représente méthyle ;
- R_6 représente H, $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ ou CO_2H ;
- R_7 représente $CH_2CH_2CO_2H$,$CH_2CH_2CO_2R$, ou

$$\begin{cases} -CH_2CH_2CO_2H \\ -H \end{cases};$$

- R_8 représente méthyle ou

$$\begin{cases} -CH_3 \\ -H \end{cases};$$

- R_9 représent H, COOH, CH_2COOH ou méthyle ;

à la condition que, lorsque R_1, R_2, R_3, R_4, R_7 et R_8 représentent deux substituants ou sont bivalents et attachés au même carbone, le noyau pyrrole r spectif auquel ils sont attachés est un dihydropyrrole ;

- R r prés nte alkyle inféri ur ou benzyle ;

avec la condition qu'au moins l'un parmi R_1-R_9 comprenne un groupe carboxyle libre, et qu des liaisons amide (1 à 4) soient formées entre l groupe amino de l'acide aminomonocarboxylique et l'un des groupes carboxyl du tétrapyrrole : avec la condition que le reste tétrapyrrole ne représent pas un **phéoph rbide a.**

2. Composition selon la revendication 1, dans laquelle l'acide aminé est un alpha amino acide.

3. Composition selon l'une des revendications 1 et 2, dans laquelle, le tétrapyrrole est une porphyrine, une chlorine ou une bactériochlorine.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle les substituants contenant un amide sont disposés de manière asymétrique sur la molécule de tétrapyrrole.

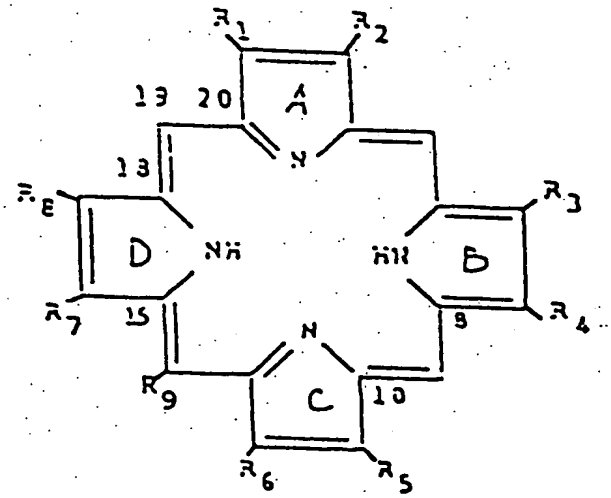
5. Composition selon la revendication 1, dans laquelle l'amide est :
- la disérinyl mésoporphyrine IX ;
- la diglycyl mésoporphyrine IX ;
- la di-α-(DL)-alanyl mésoporphyrine IX ;
- la di-β-alanyl mésoporphyrine IX ;
- la di-ε-amino-n-caproyl mésoporphyrine IX ;
- la diglycyl trans-mésochlorine IX ;
- la diglycyl trans-mésochlorine e_6 ;
- la diglycyl mésochlorine e_4 ;
- la diglycyl hématoporphyrine IX ;
- la diglycyl chlorine e_6 ;
- la diglycyl protoporphyrine IX ;
- la diglycyl deutéroporphyrine ;
- la di-α-(DL)-alanyl trans-mésochlorine IX ;
- la di-α-(DL)-alanyl mésochlorine e_6 ;
- la di-α-(DL)-alanyl mésochlorine e_4 ;
- la di-α-(DL)-alanyl hématoporphyrine IX ;
- la di-α-(DL)-alanyl chlorine e_6 ;
- la di-α-(DL)-alanyl protoporphyrine IX ;
- la di-α-(DL)-alanyl deutéroporphyrine ;
- la di-β-(DL)-alanyl trans-mésochlorine IX ;
- la di-β-(DL)-alanyl mésochlorine e_6 ;
- la di-β-(DL)-alanyl mésochlorine e_4 ;
- la di-β-(DL)-alanyl hématoporphyrine IX ;
- la di-β-(DL)-alanyl chlorine e_6 ;
- la di-β-(DL)-alanyl protoporphyrine IX ;
- la di-β-(DL-alanyl deutéroporphyrine ;
- la di-L-α-sérinyl chlorine e_6 ;
- la di-L-α-sérinyl trans-mésochlorine e_6 ;
- la di-L-α-sérinyl trans-mésochlorine IX ;
- la di-L-α-sérinyl trans-mésochlorine e_4 ;
- la di-L-α-sérinyl hématoporphyrine IX ;
- la di-L-α-sérinyl protoporphyrine IX ;
- la di-L-α-sérinyl deutéroporphyrine ;
- la di-ε-amino-n-caproyl-hématoporphyrine IX ;
- la di-ε-amino-n-caproyl-chlorine e_6 ;
- la di-ε-amino-n-caproyl-protoporphyrine IX ;
- la di-ε-amino-n-caproyl-deutéroporphyrine ;
- la mono-L-sérinyl mésochlorine e_6 ;
- la mono-L-sérinyl deutérochlorine e_6 ;
- la mono-L-sérinyl-2-formyl chlorine e_6 ;
- la mono-L-sérinyl-2-acétyl chlorine e_6 ;
- la mono-L-cystéinyl chlorine e_6 ;
- la mono-L-asparaginyl chlorine e_6 ;

- la mono sérinyl chlorine e_6 ;
- la mono-(DL) glycyl chlorin e_6 ;
- l'alanyl chlorine e_6 ;
- la mono-L-valyl chlorine e_6 ;
- la mono-L-leucyl chlorine e_6 ;
- la mono-L-isoleucyl chlorine e_6 ;
- la mono-L-prolyl chlorine e_6 ;
- la mono-L-méthionyl chlorine e_6 ;
- la mono-L-thréoninyl chlorine e_6 ;
- la tyrosyl chlorine e_6 ;
- la glutaminyl chlorine e_6 ;
- la lysyl chlorine e_6 ;
- l'arginyl chlorine e_6 ;
- l'histidyl chlorine e_6 ;
- la β-alanyl chlorine e_6 ;
- la mono-ϵ-amino-n-caproyl chlorine e_6 ;
- la monoglycyl mésoporphyrine IX ;
- la mono alanyl mésoporphyrine IX ;
- la mono-β-alanyl mésoporphyrine IX ;
- la mono-ϵ-amino-n-caproyl mésoporphyrine IX ;
- la mono-β-alanyl-hématoporphyrine IX ;
- la thréoninyl-2-formylchlorine e_6 ;
- la mono-L-thréoninyl deuterochlorine e_6 ; ou
- la mono-L-thréoninyl mésochlorine e_6.

6. Utilisation d'un mono-, di- ou polyamide fluorescent d'un acide aminomonocarboxylique et d'un tétrapyrrole contenant un ou deux groupes carboxy de la structure telle que définie à l'une quelconque des revendications 1 à 5, ou d'un sel de celui-ci, et d'un support pharmaceutiquement acceptable pour celui-ci, pour la préparation d'une composition thérapeutique pour le photodiagnostic et/ou la photothérapie de tumeurs.

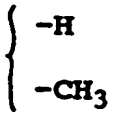
Revendications pour l'Etat contractant suivant : AT

1. Utilisation d'un mono-, di- ou polyamide fluorescent d'un acide aminomonocarboxylique et d'un composé de tétrapyrrole représenté par la formule :

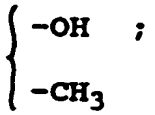


ou d'un sel de celui-ci,
ou des di- ou tétrahydrotétrapyrroles correspondants ; t d'un support pharmaceutiquement acceptable pour celui-ci ; où :

- R_1 représente méthyle,

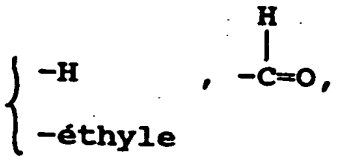


ou



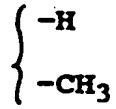
- R_2 représente H, vinyle, éthyle,

acétyle,

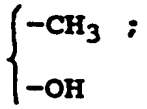


$CH_2CH_2CO_2H$, ou =CHCHO ;

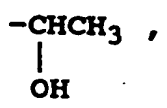
- R_3 représente méthyle,



ou



- R_4 représente H, vinyle, éthyle,



$CH_2CH_2CO_2H$, =CHCHO, ou

$$\begin{cases} -H & ; \\ -\text{éthyle} \end{cases}$$

- R_5 représente méthyle ;
- R_6 représente H, $CH_2CH_2CO_2H$, $CH_2CH_2CO_2R$ ou CO_2H :
- R_7 représente $CH_2CH_2CO_2H$,$CH_2CH_2CO_2R$, ou

$$\begin{cases} -CH_2CH_2CO_2H & ; \\ -H \end{cases}$$

- R_8 représente méthyle ou

$$\begin{cases} -CH_3 & ; \\ -H \end{cases}$$

- R_9 représente H, COOH, CH_2COOH ou méthyle ;

à la condition que, lorsque R_1, R_2, R_3, R_4, R_7 et R_8 représentent deux substituants ou sont bivalents et attachés au même carbone, le noyau pyrrole respectif auquel ils sont attachés est un dihydropyrrole ;

- R représente alkyle inférieur ou benzyle ;

avec la condition qu'au moins l'un parmi R_1-R_9 comprenne un groupe carboxyle libre, et que d s liaisons amide (1 à 4) soient formées entre le groupe amino de l'acide aminomonocarboxylique et l'un des groupes carboxyle du tétrapyrrole : avec la condition que le reste tétrapyrrole ne représente pas un **phéophorbide a.**

pour la préparation d'une composition thérapeutique pour le photodiagnostic et/ou la photothérapie d tumeurs.

2. Utilisation selon la revendication 1, caractérisée par le fait que l'acide aminé est un alpha amino acide.